Synthesis and Reactions of Aziridines *via* Batch and Flow Processes

by

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Declaration

The work in this thesis is my own independent research, and was carried out at the University of Warwick from October 2013 to January 2017. This thesis has not been submitted for a degree at any other university.

Elements of the work reported in this thesis have appeared in the scientific literature:

Hsueh, N.; Clarkson, G. J.; Shipman, M., Generation and Ring Opening of Aziridines in Telescoped Continuous Flow Processes. *Org. Lett.* **2015**, *17*, 3632.

Hsueh, N.; Clarkson, G. J.; Shipman, M., Functionalization of Alkenes through Telescoped Continuous Flow Aziridination Processes. *Org. Lett.* **2016**, *18*, 4908.

Abstract

This thesis describes the synthesis and ring opening reactions of aziridines performed under batch as well as continuous flow conditions. Chapter 1 gives a brief introduction to the synthesis and ring opening reactions of aziridines.

Chapter 2 gives a brief introduction to flow chemistry, and describes the synthesis of aziridines from 1,2-amino alcohols, as well as their subsequent ring opening reactions. Using continuous flow methodology, various aziridines were successfully synthesized in moderate to good yields. Ring opening of these aziridines with different nucleophiles was also possible in flow. These two processes could be combined in a telescoped sequence, enabling the continuous flow synthesis of functionalized products directly from the 1,2-amino alcohols, without having to isolate the aziridine intermediates.

Chapter 3 describes the aziridination of alkenes using soluble aryliminoiodanes under continuous flow. The aziridination of alkenes could be combined with further ring opening reactions *via* a telescoped, continuous flow process. This enabled the direct synthesis of ring opened products directly from the alkene, *via in situ* formed aziridines, in moderate to good yields. This second approach had broader scope than the method described in Chapter 2.

Chapter 4 reports the stereocontrolled aziridinations of alkenes with different *N*-tosyl aryliminoiodanes. Under some conditions, the asymmetric aziridination of styrene gave different enantioselectivities when the aryl group of ArI=NTs was changed. The diastereoselective aziridination of a chromene was also briefly investigated.

Chapter 5 gives a summary of the key findings, as well as possible future work.

In Chapter 6, detailed experimental procedures for the work carried out in Chapters 2 – 4 are provided.

Abbreviations

2D	2 Dimensional
Ac	Acetyl
acac	acetylacetonate
Alk	Alkyl
$[\alpha]_D$	optical rotation
Å	Angstrom
aq	aqueous
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
Bs	Benzenesulfonyl
Bu	Butyl
c	concentration
calc.	calculated
Cbz	Carboxybenzyl
COSY	Correlation Spectroscopy
δ	chemical shift
d	doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess

DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dr	diastereomeric ratio
ee	enantiomeric excess
eq	equivalent
er	enantiomeric ratio
ES^+	Electrospray (positive)
esp	α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid
Et	Ethyl
HMBC	Heteronuclear Multiple Bond Correlation
HMQC	Heteronuclear Multiple Quantum Correlation
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
hv	photoirradiation
Hz	Hertz
i	*iso*
IR	Infrared
J	coupling constant
LiHMDS	Lithium *bis*(trimethylsilyl)amide
lit.	literature
m	multiplet
M	Molar

M.p.	Melting point
m/z	mass-to-charge ratio
Me	Methyl
MHz	Megahertz
Ms	Methanesulfonyl
n	*normal*
NHC	*N*-heterocyclic carbene
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Ns	Nosyl
Nu	Nucleophile
o	*ortho*
p	*para*
Ph	Phenyl
ppm	parts per million
Pr	Propyl
pyr	pyridine
q	quartet
quint	quintet
r.t.	room temperature
R_t	Residence time
s	*sec*
s	singlet
Ses	2-(Trimethylsilyl)ethanesulfonyl
t	*tert*

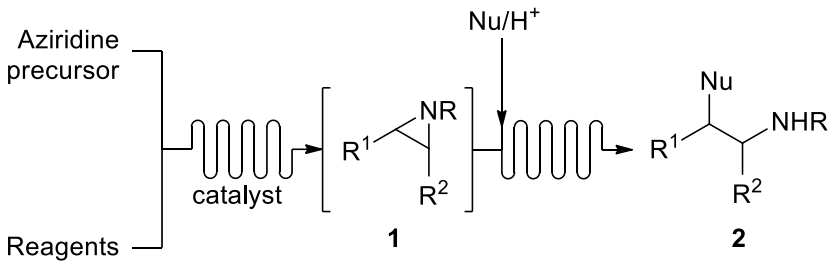
t	triplet
TBAF	Tetrabutylammonium fluoride
Tf	Trifluoromethanesulfonyl
Tol	Tolyl
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TPFC	5,10,15-*Tris*(pentafluorophenyl)corrole
TPP	Tetraphenylporphyrin
Ts	Tosyl
Xs	2-Sulfonyl-5-methylpyridine

Chapter 1:

Introduction

1.1 Aims of project

This thesis describes the synthesis and ring opening reactions of aziridines under batch and continuous flow conditions. We hoped to explore various methods to synthesize aziridines under batch conditions, and adapt these chemistries to continuous flow methodology for the first time. Ultimately we hoped to effect the *in situ* synthesis of aziridine **1** from a variety of aziridine precursors, and directly react the aziridine with nucleophiles in telescoped processes to give **2**, under continuous flow conditions (Scheme 1.1). Such new methodology has a number of potential advantages. Primarily, it would reduce the need to handle and isolate the potentially hazardous aziridines.

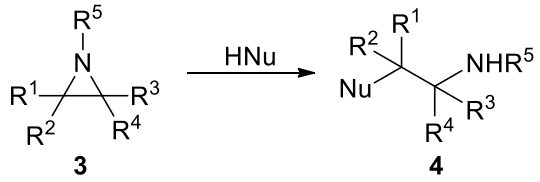


Scheme 1.1. Synthesis and ring opening of aziridine under continuous flow.

The chemistry and properties of aziridines have been extensively reviewed.[1-7] In this chapter we do not aim to exhaustively survey this work, rather to provide a summary of the relevant chemistry for the synthesis and ring openings of aziridines.

1.2 Aziridines

Aziridines (**3**) are three membered heterocycles, with a ring made up of two carbon atoms and one nitrogen atom. Aziridines are extremely important intermediates in organic chemistry, and are most commonly used as "spring loaded" electrophiles for nucleophilic ring opening reactions (Scheme 1.2).[1]



Scheme 1.2. A generalized aziridine undergoing nucleophilic ring opening.

1.3 Properties of aziridines

As a three membered ring, the internal angles of aziridines are close to 60°, compared to the normal tetrahedral (sp^3) angle of 109.5°. This introduces significant ring strain of around 27 kcal mol^{-1} to the aziridine ring.[6] Consequently, aziridines are prone to nucleophilic ring opening to relieve this ring strain.

Aziridines have a pK_a (conjugate acid) of around 8, and are less basic compared with most amines.[2] The energy required for pyramidal inversion at nitrogen is higher in aziridines, as more energy is required to promote the lone pair to a p orbital in the planar transition state during the inversion process. However, the energy barrier is still low enough that inversion occurs at room temperature if there is no electron withdrawing group on nitrogen.[2]

1.4 Biological properties of aziridines

Aziridines are prone to nucleophilic attack and are potentially powerful alkylating agents. For example the simplest aziridine, ethylenimine has been classified as being possibly carcinogenic to humans and is considered extremely hazardous due to its ability to alkylate DNA.[8] Some natural products such as Mitomycin C (**5**)[9] and Azinomycin B (**6**)[10] that contain aziridine rings are useful as antitumor agents because of their ability to cross-link DNA bases in tumors (Figure 1.1).

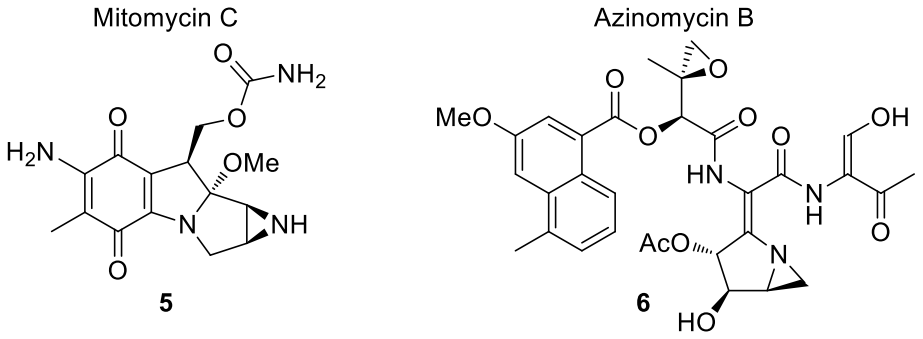
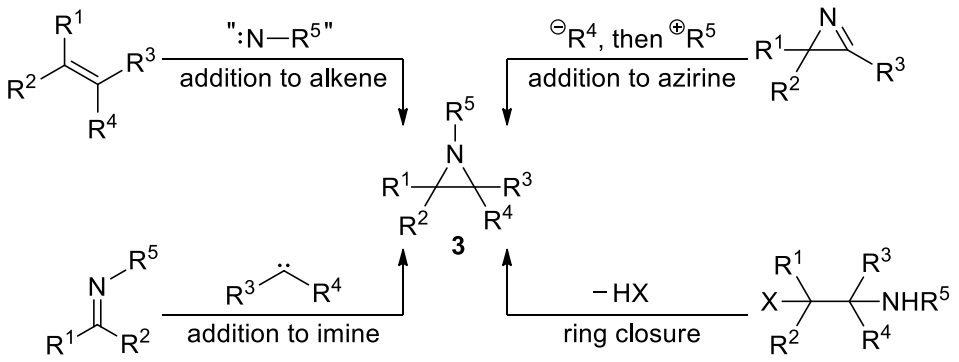


Figure 1.1. Aziridine containing natural products.

1.5 Synthesis of aziridines

Aziridines can be synthesized in four main ways: addition to alkenes, addition to imines, addition to azirines, or ring closure of 1,2-amino derivatives (Scheme 1.3).



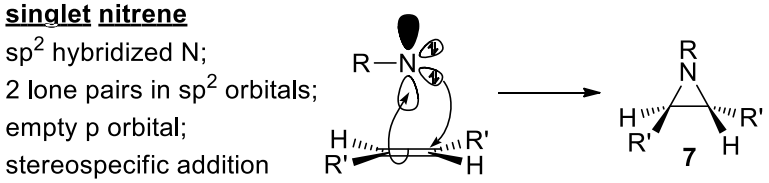
Scheme 1.3. General routes to aziridines.

1.5.1 Addition to alkenes

The synthesis of aziridines by addition to alkenes can be classified into either nitrene (or nitrenoid) methods, or non-nitrene methods. The direct aziridination of alkenes by nitrenes (or nitrenoids) is currently more popular, as conditions required are usually milder with broader substrate scope. Therefore, most of the following discussion will focus on nitrene additions, but there will be reference to non-nitrene methods when a substrate class allows comparison with non-nitrene based methods.

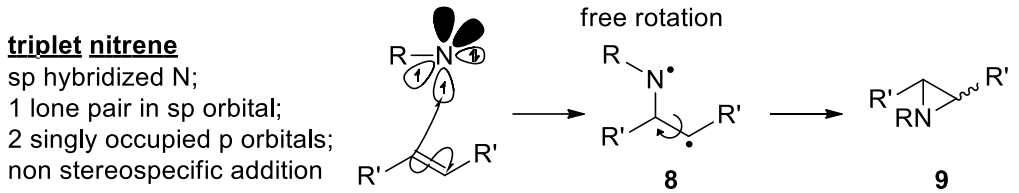
1.5.1.1 Nitrenes

Both nitrenes and nitrenoids (in which the nitrene is bound to a metal centre) can be either singlet or triplet. Singlet nitrenes (and nitrenoids) add to alkenes in a single step (but often asynchronously) to give **7** (Scheme 1.4).



Scheme 1.4. Concerted addition of singlet nitrene

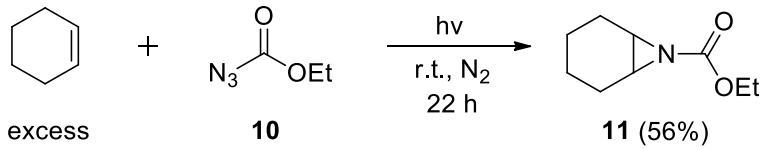
Triplet nitrenes (and nitrenoids) add stepwise to alkenes, and free rotation in the diradical intermediate **8** gives rise to a *cis*/*trans* mixture of products **9** (Scheme 1.5). Unless otherwise specified, nitrenes will be used to refer to both free nitrenes and nitrenoids in this text.



Scheme 1.5. Stepwise addition of triplet nitrene.

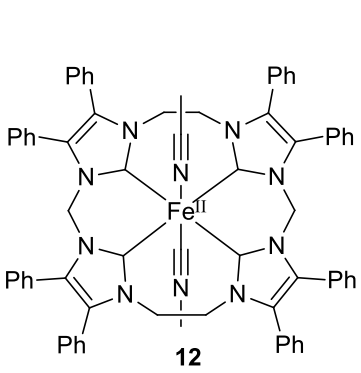
1.5.1.2 Aziridinations from organic azides

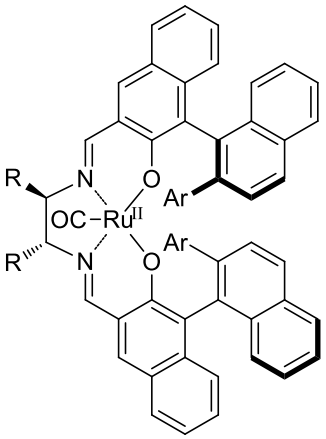
It has been known since the 1960s that the thermal or photodecomposition of acyl azides produce free nitrenes, which can undergo addition with alkenes to give aziridines. For example, Lwowski *et al.* investigated the photodecomposition of ethyl azidoformate (**10**) in cyclohexene as solvent to give the aziridine **11** (Scheme 1.6).[11-12] Based on the side products formed, he concluded that a nitrene pathway was most likely. However, due to moderate yields and side reactions, aziridinations of alkenes using organic azides as a nitrene source was not a popular method until much more recently.

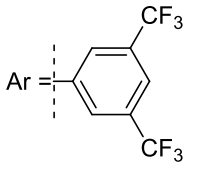


Scheme 1.6. Aziridination of cyclohexene with ethyl azidoformate.

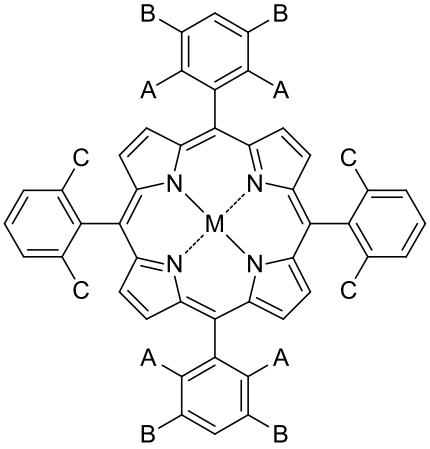
The transition metal catalysed aziridination of alkenes using organic azides as a nitrene source has gained popularity since 2000 due to concerns about atom economy and green chemistry. Using various transition metal complexes, such as **12** – **18** (Figure 1.2), both aliphatic and aromatic alkenes can be aziridinated with a range of organic azides (Scheme 1.7).







13: R, R = -(CH$_2$)$_4$-
14: R = Ph



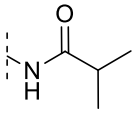
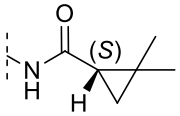
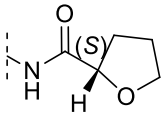
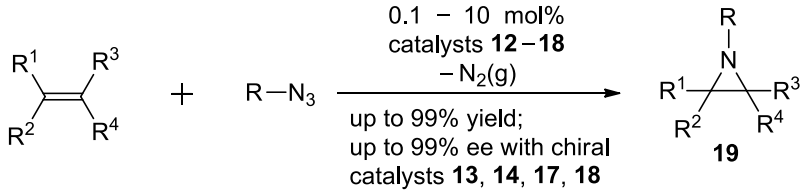
	M	A	B	C
15	Ru^{II}	H	H	H
16	Co^{II}	H	^{t}Bu	
17	Co^{II}	H	^{t}Bu	
18	Co^{II}	OMe	H	

Figure 1.2. Various catalysts used in aziridination of alkenes with organic azides.

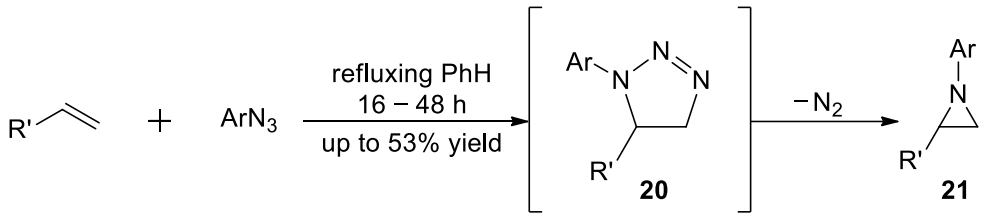


Scheme 1.7. Aziridination of alkenes with organic azides.

Jenkins *et al.* reported that using Fe^{II}(tetracarbene) complex **12**, various aliphatic alkenes could be aziridinated racemically using aryl azides as nitrene source to give aziridines in moderate to good yields.[13-14] Cenini *et al.* reported a complementary method; using Ru(TPP)CO (**15**), aromatic alkenes could be aziridinated to give racemic *N*-aryl aziridines in moderate to good yields.[15-16]

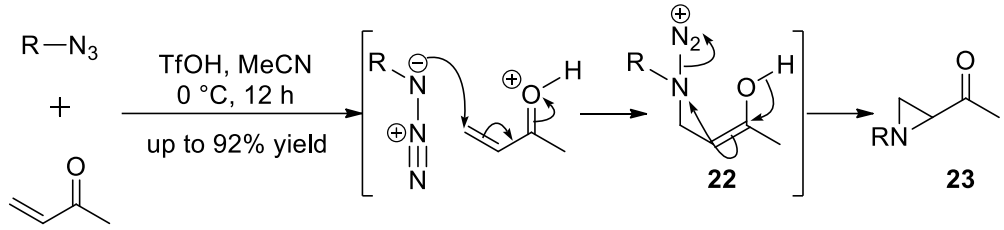
Katsuki *et al.* reported the asymmetric synthesis of *N*-sulfonylaryl aziridines from aromatic alkenes to give aziridines in moderate to good yields and high ee using Ru(salen) complex **13**.[17] Using Ru(salen) complex **14**, Katsuki *et al.* effected the asymmetric synthesis of both aromatic and aliphatic *N*-Ses aziridines in high yields and ee.[18] Zhang *et al.* have also investigated the aziridination of alkenes using organic azides as nitrene source using Co^{II}(porphyrin) complexes **16** – **18** giving a broad range of *N*-sulfonyl and *N*-phosphoryl aziridines both racemically[19] and asymmetrically.[20-21]

Organic azides can also form aziridines by non-nitrene methods. For example, alkenes can undergo 1,3-dipolar cycloadditions with aryl azides to give the 1,2,3-triazoline **20** which can lose nitrogen to give aziridine **21** (Scheme 1.8).[22-23] However, yields are moderate, and this is not a popular method.



Scheme 1.8. Aziridines from cycloaddition with azides, followed by loss of N_2.

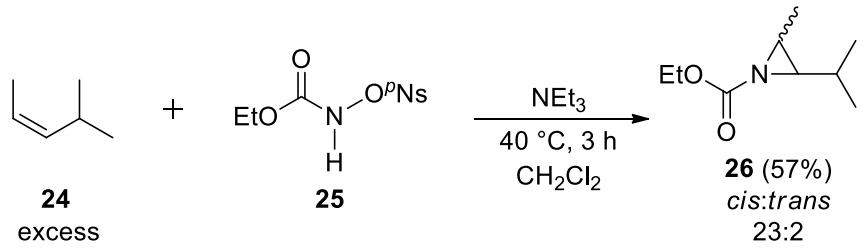
Organic azides can also undergo conjugate addition with alkenes conjugated with a carbonyl group, and loss of nitrogen gives the aziridine. For example, Johnston *et al.* reported that various alkyl azides could undergo conjugate addition with but-3-en-2-one under TfOH catalysis, and ring closure *via* intermediate **22** gives aziridine **23** in moderate to good yields (Scheme 1.9).[24]



Scheme 1.9. Aziridination of but-3-en-2-one.

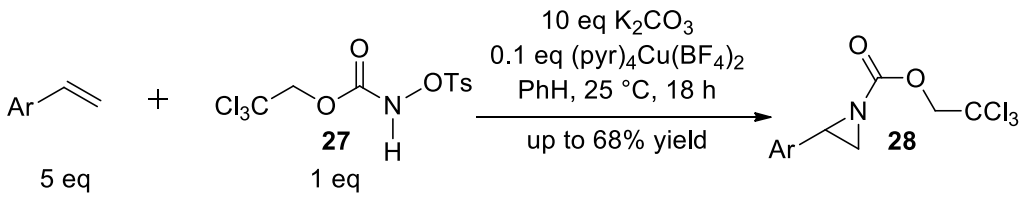
1.5.1.3 Aziridinations by α-elimination

Nitrenes can also be generated from the α-elimination of certain organic substrates such as ethyl (4-nitrobenzenesulfonyloxy)carbamate **25** or haloamine salts. In 1967, as part of an investigation into the properties of singlet and triplet nitrene, Lwowski *et al.* reported that a *cis*/*trans* mixture of aziridine **26** was produced when *cis*-alkene **24** was reacted with **25** in the presence of NEt_3 (Scheme 1.10).[25]



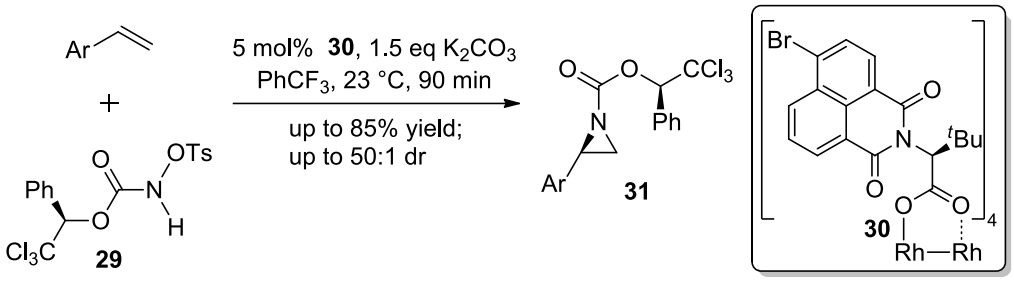
Scheme 1.10. Aziridination from α-elimination.

More recently, Lebel *et al.* reported that styrene derivatives are aziridinated in moderate to good yields from the α-decomposition of *N*-tosyloxycarbamate **27** in the presence of $(pyr)_4Cu(BF_4)_2$ (Scheme 1.11.).[26]



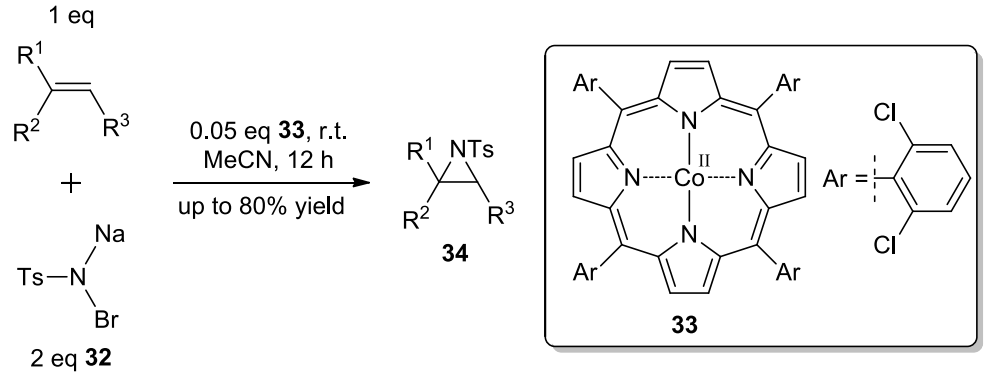
Scheme 1.11. Lebel *et al.*'s aziridination with *N*-tosyloxycarbamate **27**.

Using chiral *N*-toxyloxycarbamate **29** and a chiral Rh(II) complex **30**, styrene derivatives could be aziridinated in good yields with moderate to high dr, using the alkene as the limiting reagent (Scheme 1.12).[27] However, neither of these methods worked with aliphatic alkenes.



Scheme 1.12. Lebel *et al.*'s stereoselective aziridinations.

Zhang *et al.* investigated the racemic aziridinations of both aromatic and aliphatic alkenes using bromamine-T (**32**) and Co(II)[28] or Fe(II)[29] metalloporphyrins. They found that Co(II) porphyrin complex **33** was extremely efficient at catalysing the aziridination, and required only 1 eq of the alkene (Scheme 1.13).

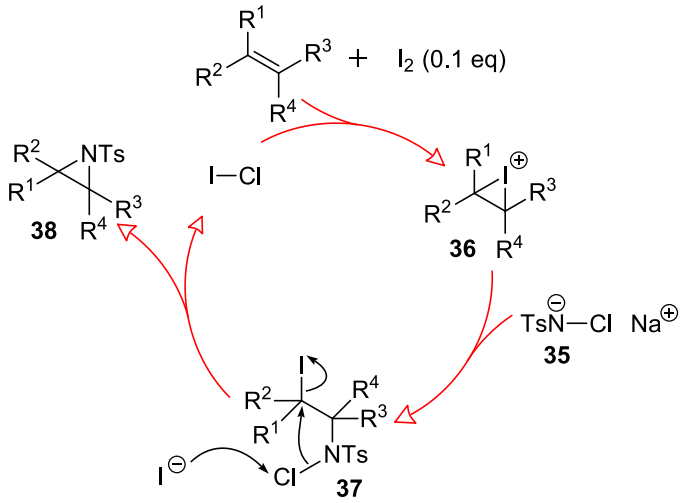


Scheme 1.13. Zhang *et al.*'s aziridination with bromamine-T.

Chloramine-T (**35**) can also be used as a nitrene source for the aziridination of aliphatic and aromatic alkenes, instead of bromamine-T. Komatsu *et al.* reported that CuCl as well as other copper salts such as $CuCl_2$, $Cu(acac)_2$, $Cu(OTf)_2$ catalysed the nitrene transfer from anhydrous chloramine-T to various alkenes.[30]

In the absence of copper salts, no aziridine was formed. Other methods for aziridination of alkenes *via* nitrene transfer from chloramine-T using other transition metal salts such as Fe(IV)[31] or Ag(I)[32] have been reported.

Chloramine-T is also known to aziridinate alkenes by non-nitrene pathways. In the presence of a positive bromine or iodine source such as iodine[33] or *N*-bromosuccinimide,[34] attack of chloramine-T on the cation **36** followed by cyclization of **37** gives the aziridine **38** (Scheme 1.14); both aliphatic and aromatic *N*-tosyl aziridines can be synthesized by this method.

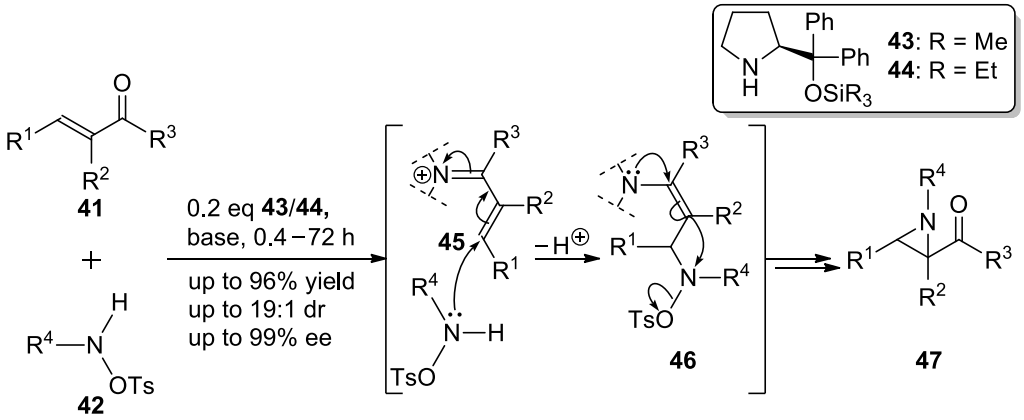


Scheme 1.14. Iodine catalysed aziridine synthesis.

Closely related to these haloamine salts **32** and **35** are *N*,*N*-dichloroamine-T (**39**) and *N*,*N*-dibromoamine-T (**40**) (Figure 1.3). Both can be used to synthesize *N*-tosyl aziridines from alkenes, but whether a halonium, radical, or nitrene mechanism is involved is a contested issue.[35-40]

Figure 1.3. *N*,*N*-dihaloamine-T **39** and **40**.

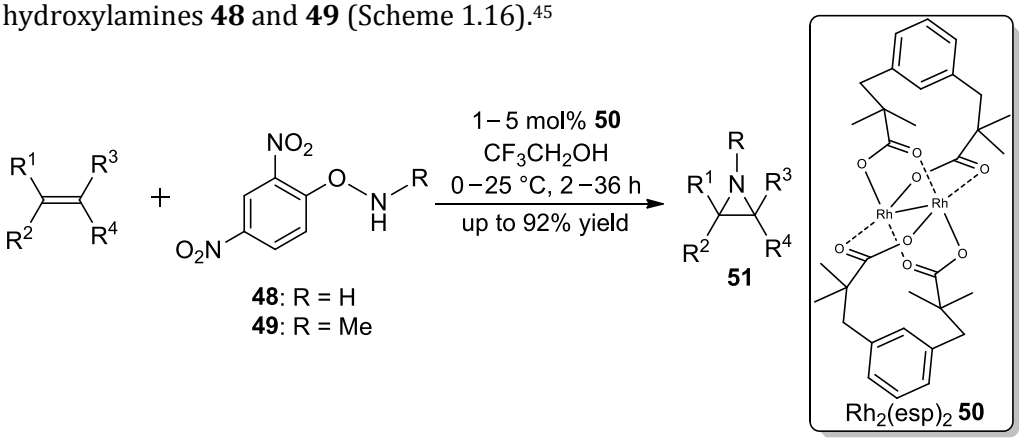
A number of reagents that could undergo α-elimination can undergo conjugate addition with α,β-unsaturated aldehydes and ketones. These reactions are often organocatalyzed by chiral amines such as **43** and **44**, with high stereoselectivity and yields. The mechanism proceeds through an iminium intermediate **45** (Scheme 1.15). Cordova *et al.* investigated the asymmetric synthesis of aziridines from various α,β-unsaturated aldehydes and found that high yields and ee could be obtained with proline-derived chiral amine catalysts.[41] Other chiral amines can also be used,[42] but derivatives based on proline are the most common.[43-44]



Scheme 1.15. Synthesis of aziridines from α,β-unsaturated aldehydes and ketones.

1.5.1.4 Aziridinations with amines

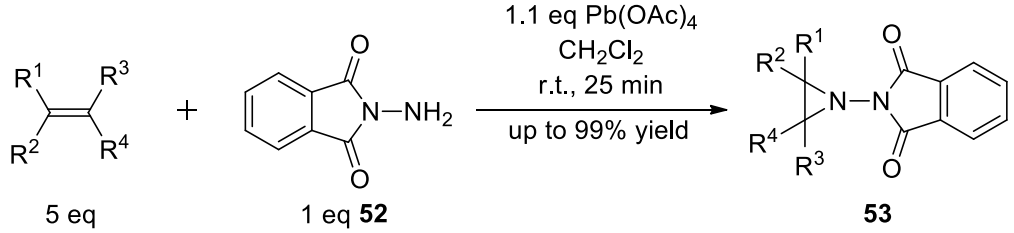
Recently, Jat *et al.* reported the $Rh_2(esp)_2$ catalysed aziridination of alkenes, using hydroxylamines **48** and **49** (Scheme 1.16).[45]



Scheme 1.16. Jat *et al.*'s aziridination with hydroxylamines.

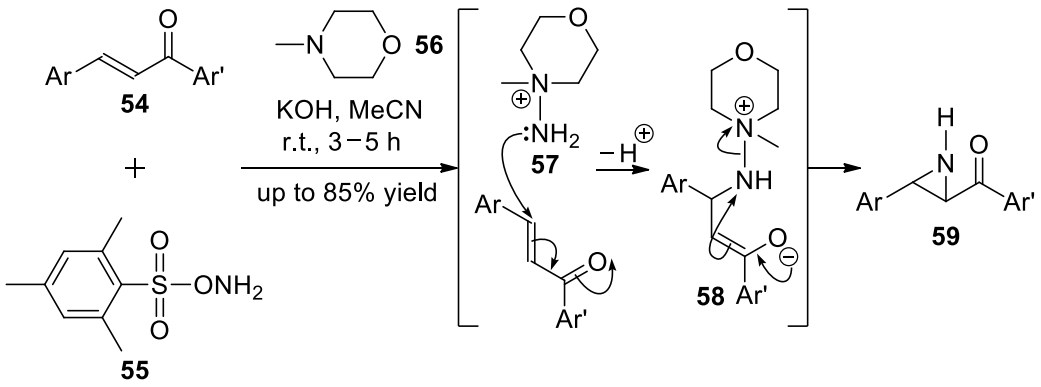
Both aliphatic and aromatic alkenes could be aziridinated to give the *N*H and *N*Me aziridines in good yield. Jat *et al.* reported that the evidence pointed to a Rh-nitrene pathway.[45]

N-Amino heterocycles such as **52** can form aziridines with alkenes in the presence of $Pb(OAc)_4$ (Scheme 1.17). These reactions were originally thought to involve a nitrene intermediate,[46-47] but this is no longer thought to be the case.[48-49] Work to understand the exact mechanism is still ongoing.[50] However, these reactions are of limited value due to the high toxicity of $Pb(OAc)_4$.



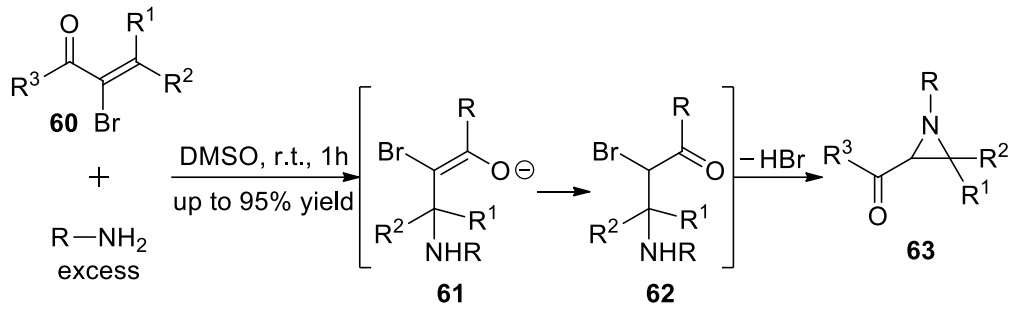
Scheme 1.17. Synthesis of aziridines with $Pb(OAc)_4$.

Aziridines can also be synthesized from chalcones. Shi *et al.* reported that hydroxylamine **55** is capable of synthesizing *N*H aziridine **59** from chalcone **54** in the presence of *N*-methylmorpholine (**56**) through addition of *in situ* formed hydrazinium **57** (Scheme 1.18).[51]



Scheme 1.18. Shi *et al.*'s synthesis of aziridines from chalcones.

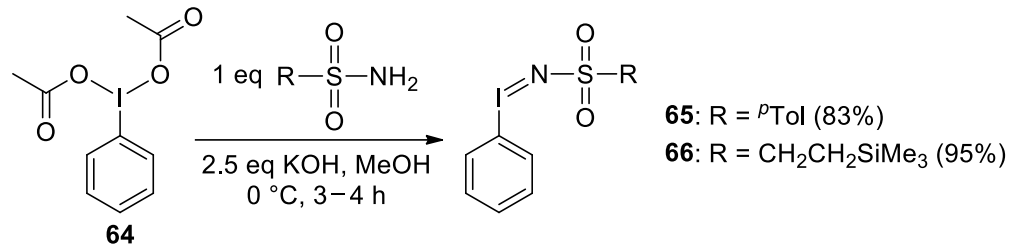
Cardillo *et al.* explored the Gabriel-Cromwell conjugate addition of amines with α,β-unsaturated α-bromo carbonyl compound **60** (Scheme 1.19).[52] Addition of the amine gives **61**, which yields aziridine **63** after cyclization of **62**. This method has been extended to diasterocontrolled aziridine synthesis through use of chiral auxiliaries or chiral amines.[53-54]



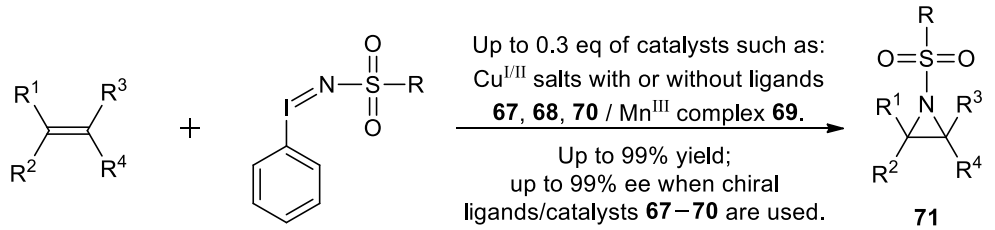
Scheme 1.19. Aziridines by Gabriel-Cromwell reactions.

1.5.1.5 Aziridinations with phenyliminoiodanes

N-(Tosyl)iminophenyliodinane (PhI=NTs, **65**) was first prepared by Okawara *et al.* in 1975 (Scheme 1.20).[55] Since then, other PhI=NSO_2R derivatives have been prepared from sulfonamides.[56-57] The most popular and frequently used iminoiodanes are PhI=NTs (**65**) and PhI=NSes (**66**). These PhI=NSO_2R derivatives are capable of acting as a nitrene source for the aziridination of alkenes in the presence of transition metal catalysts (Scheme 1.21).[58-59] If chiral ligands[60-62] or catalysts[63] (Figure 1.4) are used, enantioselectivity can be achieved. Aromatic alkenes tend to give better yields compared to aliphatic alkenes.



Scheme 1.20. Preparation of PhI=NSO_2R.



Scheme 1.21. Aziridinations of alkenes with $PhI{=}NSO_2R$.

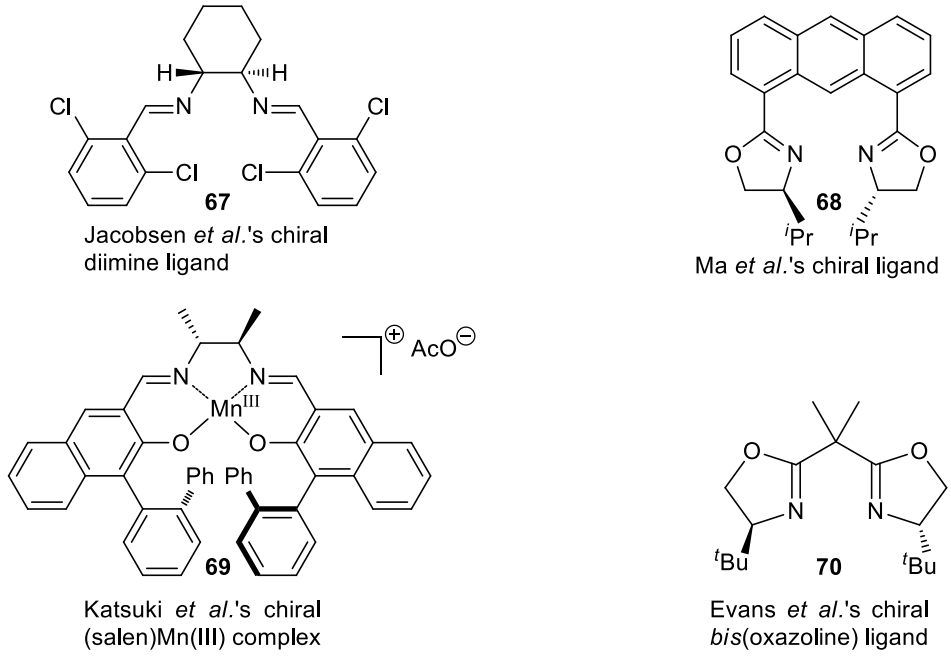


Figure 1.4. Some chiral ligands and catalysts used with $PhI{=}NSO_2R$.

Aziridinations can be done with either alkene or $PhI{=}NSO_2R$ as the limiting reagent. However, a large excess of alkene is often used to get the best yields. These reactions can be done racemically with $Cu^{I/II}$ salts, or asymmetrically when chiral ligands such as those developed by Jacobsen,[60] Ma,[61] or Evans[62] *et al*. are used together with $Cu^{I/II}$ salts. Manganese complexes, such as those developed by Katsuki *et al.*[63] can also be used for aziridinations of alkenes.

A major limitation with aziridinations by this method is that the aziridine nitrogen has to have an arylsulfonyl group on it. However, *N*Ses aziridines are also accessible, making sulfonamide removal more facile.[57]

It is not always necessary to isolate the iodinane, and there are examples in literature where the $PhI{=}NSO_2R$ is generated *in situ* from RSO_2NH_2 and $PhI(OAc)_2$.[64-66]

1.5.2 Addition to imines

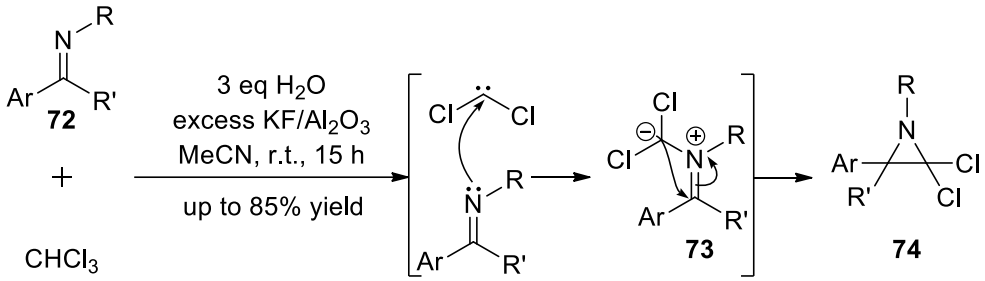
As with additions to alkenes to give aziridines, additions to imines can either involve carbene (or carbenoid) or non-carbene methods. The reagents used to generate both types of intermediates can be the same, with conditions, catalysts and substrates dictating whether a carbene (or carbenoid) is involved in addition.

1.5.2.1 Carbenes

As with nitrenes, carbenes can also exist in the singlet and triplet states. However, while the distinction between singlet and triplet state carbenes is important in cyclopropanation reactions, most reactions with imines appear to involve the carbene behaving as if it were in the singlet state. As with nitrenes, carbenes can exist as both free carbenes or as metal-bound carbenoids.

1.5.2.2 Additions from α-elimination of chloroform

The addition of free dichlorocarbene ($:CCl_2$) generated from the alkoxide induced α-elimination of $CHCl_3$ to imines to give aziridines has been known since the 1950s.[67] Recently, Komatsu *et al.* reported use of KF/Al_2O_3 as a solid supported base for the generation of dichlorocarbene to aziridinate *C*-aryl imine **72** (Scheme 1.22).[68]

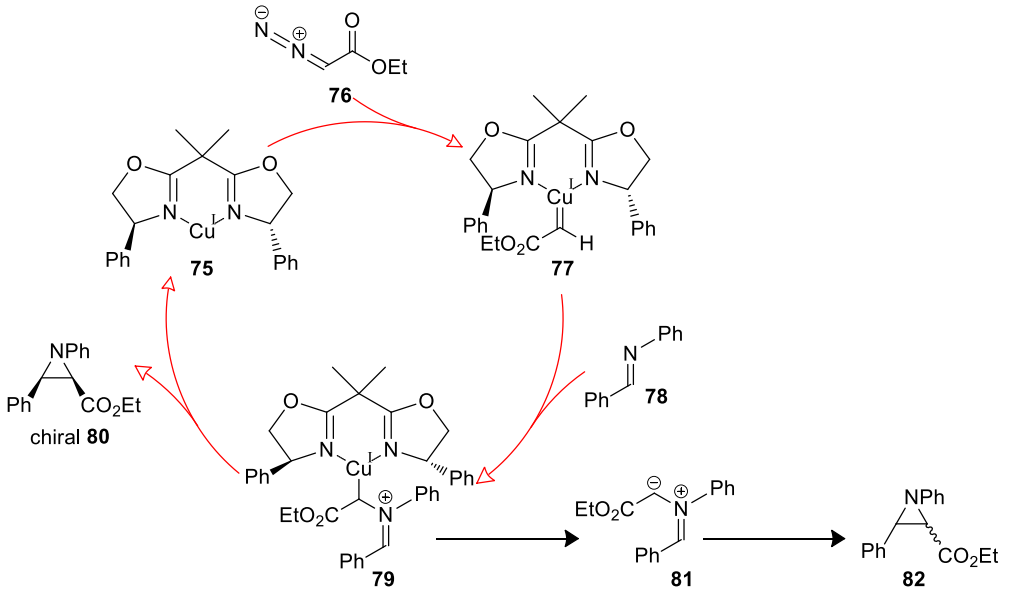


Scheme 1.22. Komatsu *et al.*'s aziridination of imines with dichlorocarbene.

The reaction is thought to proceed by addition of the lone pair of the imine to dichlorocarbene to give ylide **73**, which ring closes to give aziridine **74**.[69] Other methods for aziridination with dichlorocarbene involve phase transfer catalyst.[70-72] Examples of aziridinations involving *C*-alkyl imines and dichlorocarbene are extremely rare.[73]

1.5.2.3 Additions from diazo compounds

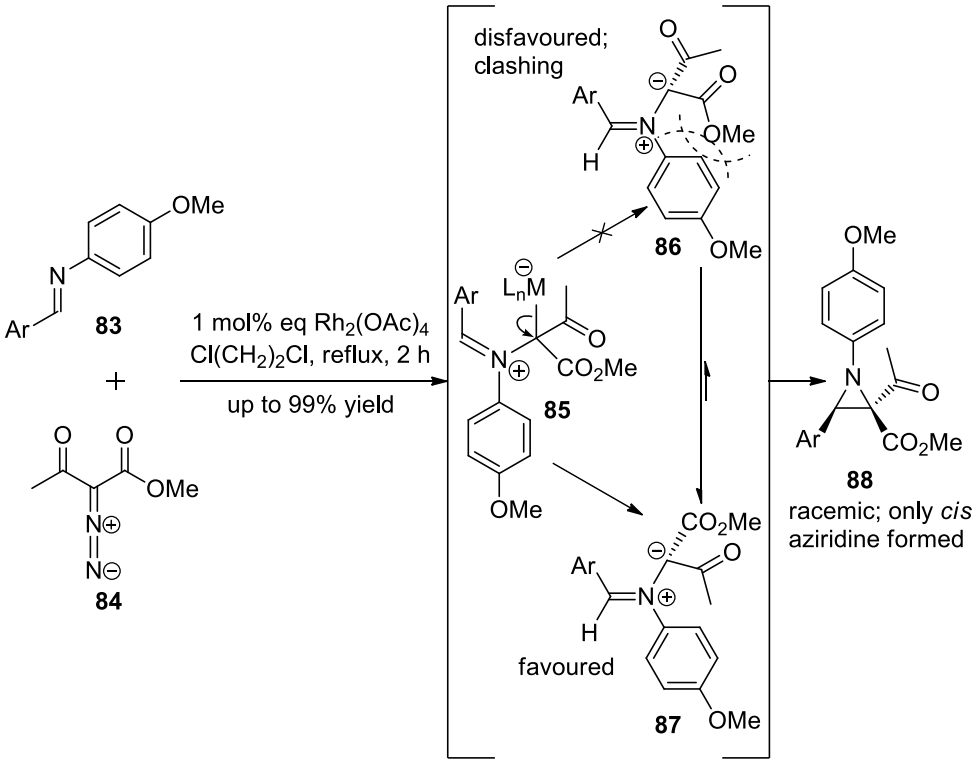
In 1995, Jacobsen *et al.* reported the enantioselective aziridination of imines with ethyl diazoacetate using copper(I) complexed to *bis*(oxazoline) ligand **75** (Scheme 1.23).[74]



Scheme 1.23. Proposed mechanism for Cu^{I} catalysed carbenoid transfer to imines.

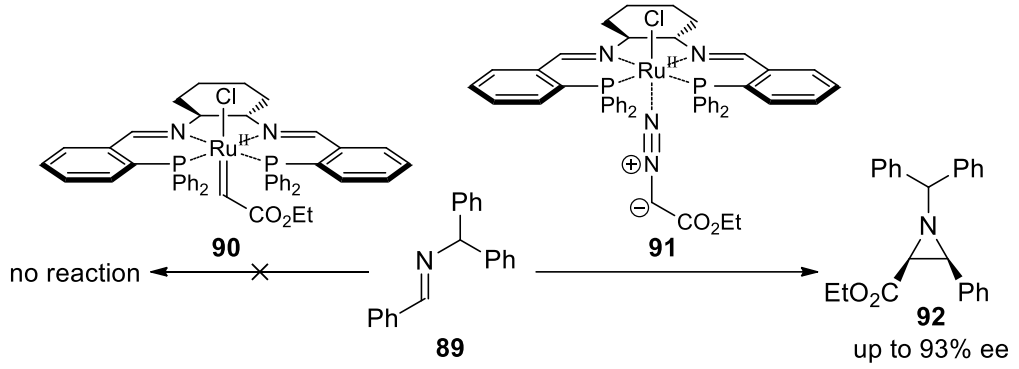
Jørgensen *et al.* reported a similar but racemic process using $Cu(OTf)_2$ without the chiral ligand.[75] In both cases, a *cis*/*trans* mixture of aziridines was formed; with Jacobsen's asymmetric carbenoid transfer, yields were low and the ee of the *cis*/*trans* aziridines formed moderate. Jacobsen rationalized this by proposing that chiral intermediate **79** could dissociate to give achiral **81**, which would then cyclize to give a racemic mixture of *cis*/*trans* aziridine **82**.

Rh(II) complexes known to catalyse the cyclopropanation of aromatic alkenes with diazo compounds have also been investigated in the aziridination of imines.[76] In an interesting example, Zhang *et al.* reported the highly diastereoselective synthesis of *cis*-aziridines from imine **83** (Scheme 1.24).[77] They rationalized this selectivity by considering the relative stability of presumed intermediates **86** and **87**.



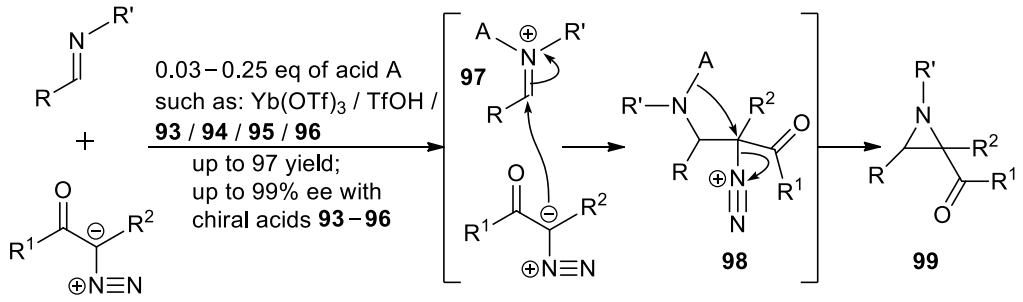
Scheme 1.24. Zhang *et al.*'s aziridination of imine.

Other transition metal catalysed aziridination of imines may not involve carbene transfer.[78-79] Mezzetti *et al.* reported that Ru(II) complex **91** effected the synthesis of aziridine **92** from imine **89** but carbene complex **90** failed to give any aziridine (Scheme 1.25).[80] These authors proposed that for some transition metal catalysed reactions of imines with ethyl diazoacetate, the transition metal might be increasing the nucleophilicity of ethyl diazoacetate towards nucleophilic attack on the imine, rather than directly forming a carbene complex.



Scheme 1.25. Reaction of imine **89** with Ru(II) complexes.

Another approach to the synthesis of aziridines from imines and diazocompounds involves using Lewis or Brønsted acid catalysis. In this approach, the imine coordinates to the acid first to form a charged iminium **97**, which is activated towards attack by the carbon of the diazo compound (Scheme 1.26). Loss of N_2 from the intermediate **98** then gives the aziridine **99**.[81-82] Asymmetric variants are possible with chiral acid catalysts (Figure 1.5).[83-88]



Scheme 1.26. Acid-catalyzed aziridine synthesis with achiral diazo compounds.

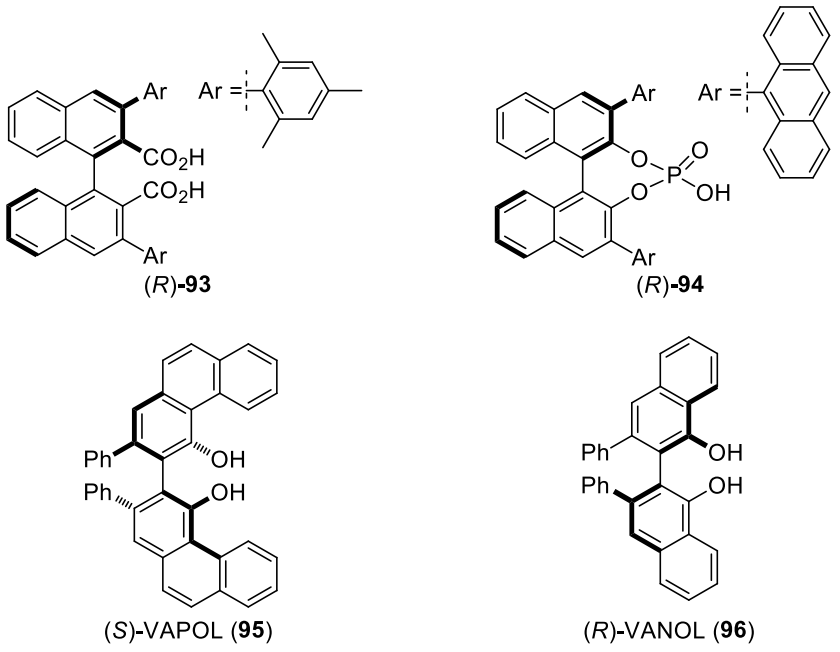
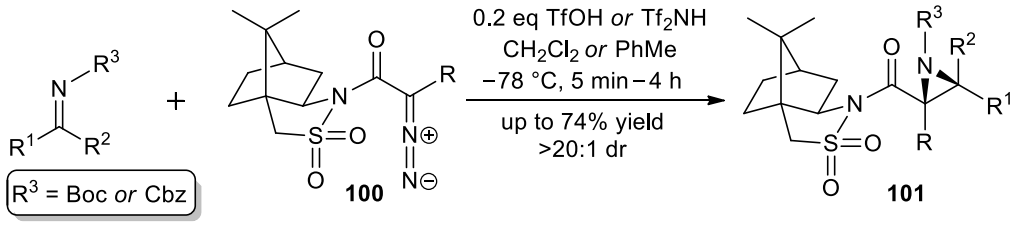


Figure 1.5. Various chiral acids/ acid precusors.

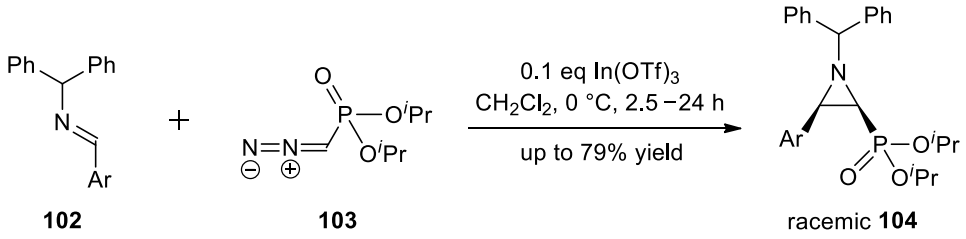
Jørgensen *et al.* investigated the synthesis of racemic *cis*-aziridines from *N*-aryl imines using Lewis acids such as $Yb(OTf)_3$.[81] Johnston *et al.* found that using TfOH as Brønsted acid allowed the synthesis of *N*-alkyl *cis*-aziridines in moderate to good yields.[82] Using chiral Brønsted acid (*R*)-**93**, Maruoka *et al.* found that *N*-Boc *trans*-aziridines were synthesized in moderate to good yields with high ee.[83] In closely related work, Zeng *et al.* found that chiral phosphoric (*R*)-**94** gave chiral *N*-Boc *trans*-aziridines with high yields and ee.[84] Another approach pioneered by Wulff *et al.* is based on chiral Lewis acids derived from (*S*)-VAPOL (**95**) or (*R*)-VANOL (**96**).[85-88] Both give high yields and ee, with up to 50:1 preference for the *cis*-aziridine from *N*-alkyl imines.

An alternative approach to using chiral acid catalysts in order to effect enantioselectivity is to use a chiral auxiliary on the diazo compound. Using the chiral diazo compound **100**, Maruoka *et al.* synthesized aziridine **101** in moderate to high yield with more than 20:1 dr (Scheme 1.27).[89]



Scheme 1.27. Maruoka *et al.*'s synthesis of chiral aziridines.

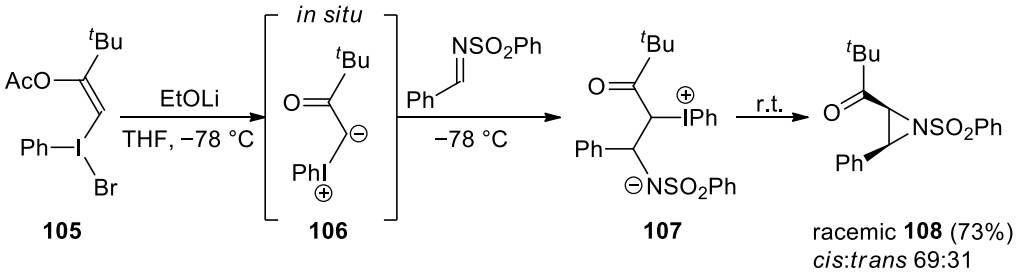
The synthesis of aziridines from imines using diazo compounds without a carbonyl group is not as well explored.[90-91] Pellicciari *et al.* reported an $In(OTf)_3$ catalyzed synthesis of *cis*-aziridine **104** with diisopropyl diazomethylphosphonate (**103**) from *C*-aryl imine **102** (Scheme 1.28).[91]



Scheme 1.28. Pellicciari *et al.*'s synthesis of *cis*-aziridines.

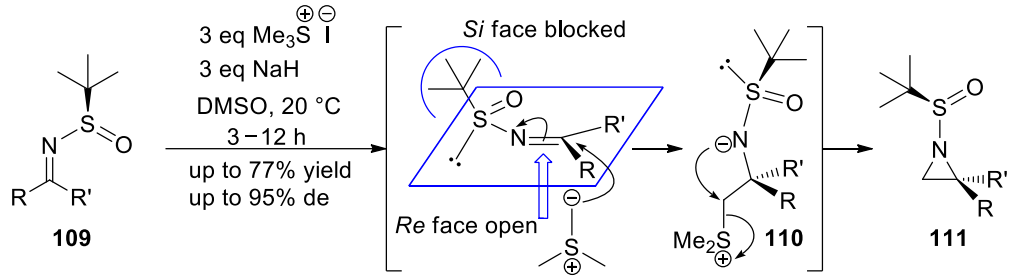
1.5.2.4 Additions of ylides

The reaction of ylides with imines is another useful approach to synthesize aziridines. While the synthesis of aziridine **108** was reported by Ochiai *et al.*[92] using *in situ* generated iodonium ylide **106** (Scheme 1.29), the usage of sulfur ylides has attracted a lot more attention.



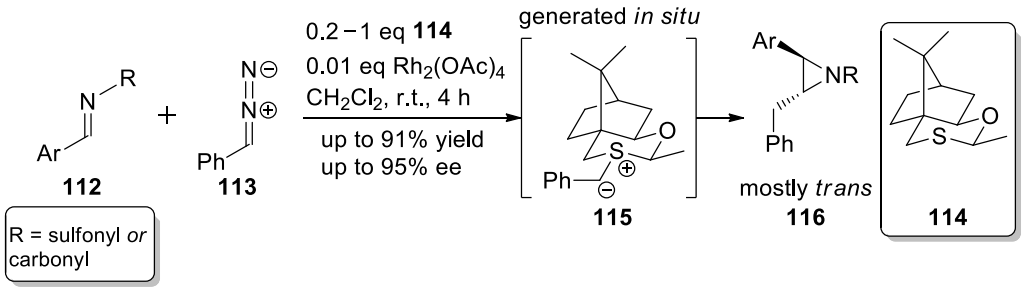
Scheme 1.29. Ochiai *et al.*'s racemic synthesis of aziridines with ylide **106**.

Ruano[93-94] and Davis[95] independently investigated the synthesis of aziridines from various chiral sulfinyl imines with sulfur ylides. Later work by Stockman established that chiral *t*-butylsulfinyl imine **109** gave the best diastereoselectivities.[96-97] High yields and de could be obtained with *C*-aryl or *C*-alkyl imine **109** (Scheme 1.30). The diastereoselectivity was rationalized by attack of the sulfur ylide onto the *Re* face, opposite to the *t*-butyl group.



Scheme 1.30. Stockman *et al.*'s synthesis of aziridines from sulfinylimine **109**.

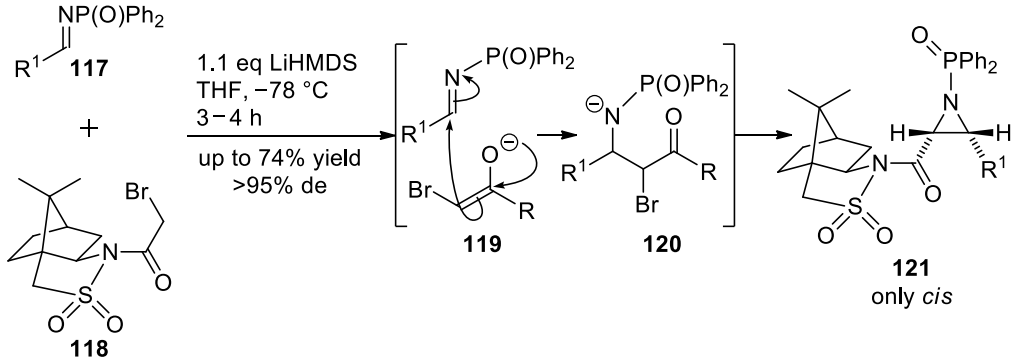
Another approach to sulfur ylide additions to imines is to use a chiral sulfur ylide.[98-99] Aggarwal *et al.* reported using chiral sulfide **114** as a catalyst for the enantioselective synthesis of chiral, *trans*-aziridine **116**. Various *C*-aryl imines with *N*-sulfonyl or *N*-carbonyl protecting groups can be used (Scheme 1.31).[98] In this method, $Rh_2(OAc)_4$ catalyzed a carbene transfer from **113** to **114** to give the sulfur ylide **115** *in situ*, which then reacts with the imine **112**.



Scheme 1.31. Aggarwal *et al.*'s asymmetric synthesis of aziridines with chiral sulfide **114**.

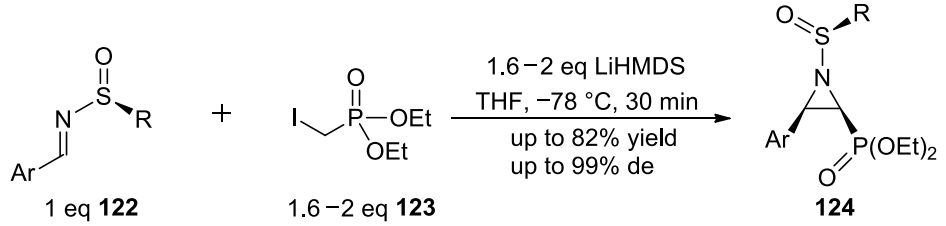
1.5.2.5 Additions of anions with a leaving group

The addition of anions with leaving groups onto imines follows a similar mechanism to that described for ylides in 1.5.2.4., and ring closure *via* loss of the leaving group gives the aziridine. The synthesis of aziridines by addition of α-haloenolates to imines was first reported by Deyrup, albeit with unpredictable diastereoselecivity.[100-101] Approaches using chiral α-haloenolates[102-103] or chiral sulfinylimines[104] have been developed, with improved diastereoselectivity. For example, Sweeney *et al.* reported the synthesis of *N*-diphenylphosphinyl *cis*-aziridine **121** from *N*-diphenylphosphinyl imine **117** with almost complete diastereocontrol in good yields (Scheme 1.32).[102-103]



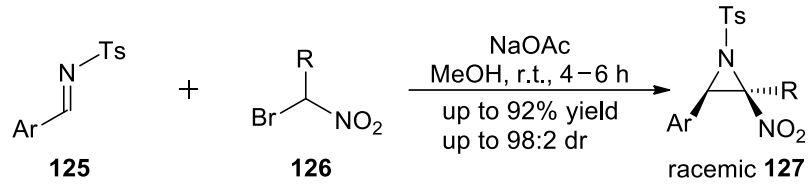
Scheme 1.32. Sweeney *et al.*'s synthesis of aziridine using chiral α-haloenolate.

Other anions with leaving groups can also add to imines and form aziridines by loss of the leaving group. For example, Davis *et al.* reported that the anion derived from iodophosphonate **123** reacted with *N*-sulfinyl imine **122** to give *cis*-aziridine **124** in high yields and de (Scheme 1.33).[105-106]



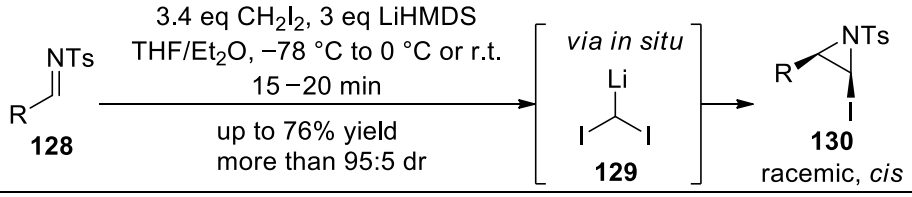
Scheme 1.33. Davis *et al.*'s synthesis of 2-phosphonate *cis*-aziridines.

Yadav *et al*. reported that 1-bromoalkane **126** reacted with *N*-tosyl imine **125** to give racemic aziridine **127**, with high diastereoselectivity for the aryl group *cis* to NO_2 (Scheme 1.34).[107]



Scheme 1.34. Yadav *et al.*'s racemic synthesis of aziridines with 1-bromoalkane **126**.

Bull *et al.* reported the diastereoselective synthesis of aziridines with $LiCHI_2$ (**129**).[108-109] They found that *N*-tosyl imine **128** could be reacted with *in situ* generated $LiCHI_2$ to give racemic *C*-iodo *cis*-aziridine **130** (Scheme 1.35).[109]



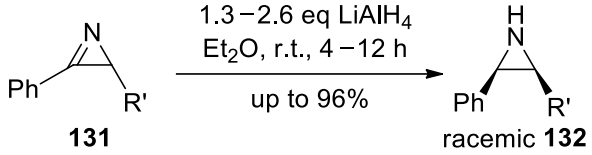
Scheme 1.35. Bull *et al.*'s synthesis of *C*-iodo *cis*-aziridines.

1.5.3 Addition to azirines

Aziridine synthesis from azirines can proceed by three main pathways: by addition of nucleophiles, by addition of radicals, or by [4+2] cycloadditions with dienes.

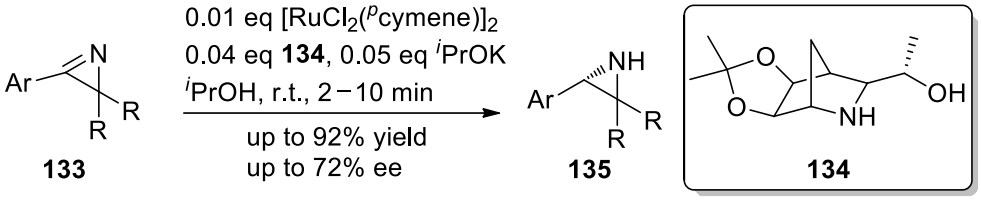
1.5.3.1 Addition of nucleophiles

Using reagents such as $LiAlH_4$ or $NaBH_4$, it is possible to stereospecifically add hydride to the less hindered face of the azirine to give the *cis*-aziridine preferentially.[110-112] For example, Hassner *et al.* reported that racemic azirine **131** could be reduced with $LiAlH_4$ to give *cis*-aziridine **132** in high yields (Scheme 1.36).[110]



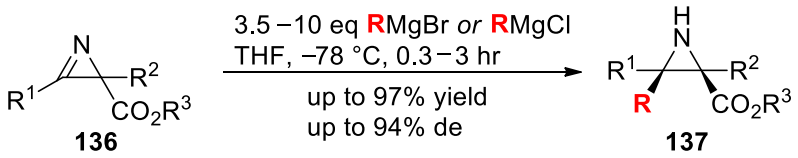
Scheme 1.36. Hassner *et al.*'s addition of hydride to azirines.

Additionally, using asymmetric transfer hydrogenation, Somfai *et al.* reported achiral azirine **133** can be hydrogenated to give chiral aziridine **135** in up to 72% ee using ^{i}PrOH as the hydrogen donor (Scheme 1.37).[113]



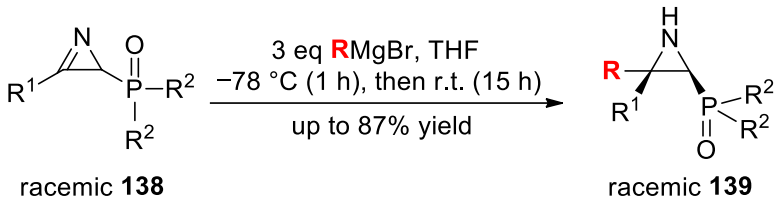
Scheme 1.37. Somfai *et al.*'s asymmetric transfer hydrogenation of azirines.

Interestingly, when Grignard reagents are added to azirines bearing an ester group on the sp^3 carbon, Davis *et al.* found that the reagent added from the more hindered face of **136**, syn to the ester group (Scheme 1.38).[114-115] They rationalized this was due to chelation of the organometallic reagent to the carbonyl oxygen.



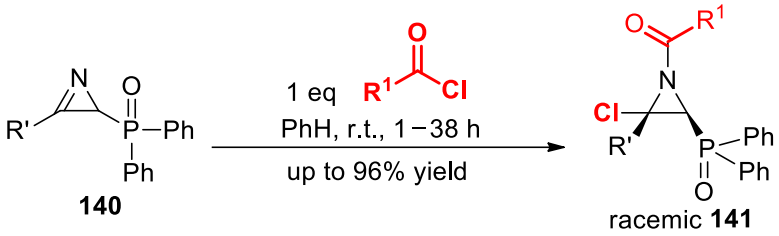
Scheme 1.38. Davis *et al.*'s addition of Grignard reagents to azirines.

Palacios *et al.* found that when the ester group is replaced with a phosphonate group, Grignard reagents add from the less hindered face, away from the phosphonate group (Scheme 1.39).[116] This is typical with most other nucleophiles, which usually add from the less hindered face of the azirine.[117-118]



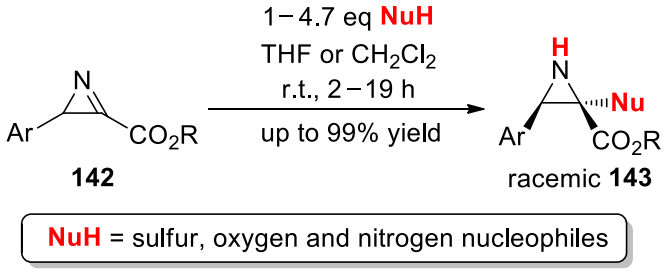
Scheme 1.39. Palacios *et al.*'s addition of Grignards to azirines.

Palacios *et al.* reported that azirine **140** could be acylated with subsequent addition of chloride from the less hindered face giving *trans*-aziridine **141** (Scheme 1.40).[119]



Scheme 1.40. Palacios *et al.*'s addition of chloride to azirines.

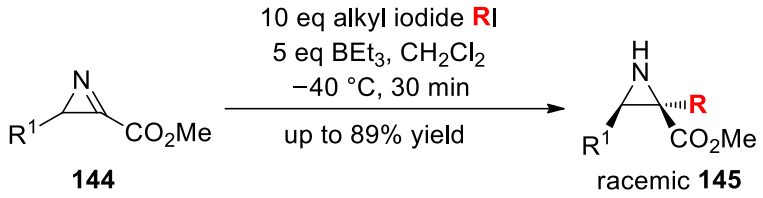
Alves *et al.* explored the addition of various nucleophiles to azirine **142** and found that sulfur, oxygen and nitrogen nucleophiles added from the less hindered face to give the *trans*-aziridine **143** (Scheme 1.41).[120] They also explored the addition of nucleophiles to azirines containing a chiral auxiliary; however, diasteroselectivity was good only using aromatic thiols as nucleophiles.[121]



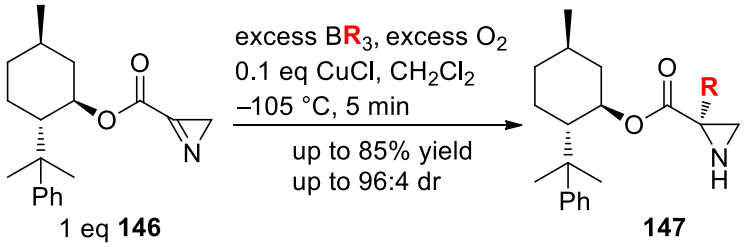
Scheme 1.41. Alves *et al.*'s synthesis of azirdines by addition of NuH.

1.5.3.2 Addition of radicals

The addition of alkyl radicals to azirines is a useful way to synthesis aziridines. Alves *et al.* reported that alkyl radicals R· added to azirine **144** from the less hindered face with a high degree of stereoselectivity, giving aziridine **145** (Scheme 1.42).[122] Somfai *et al.* investigated the addition of various alkyl radicals to azirines with a chiral auxiliary, and found chiral azirines derived from 8-phenyl-menthol gave the best diastereoselectivities (Scheme 1.43).[123-124]



Scheme 1.42. Alves *et al.*'s addition of alkyl radicals to azirine **144**.

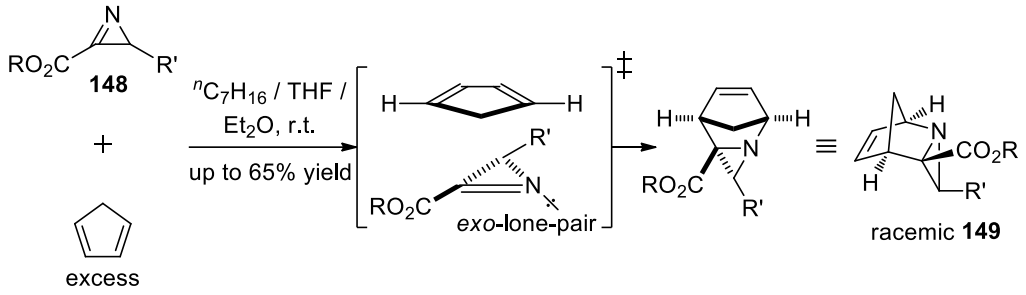


Scheme 1.43. Somfai *et al.*'s addition of alkyl radicals to chiral azirine **146**.

1.5.3.3 Cycloaddition with dienes

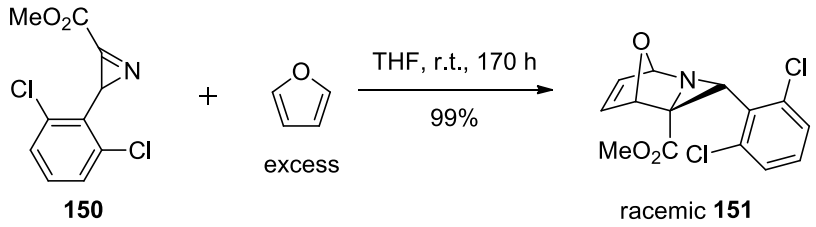
Azirines with a carboxyl substituent at the sp^2 carbon of the azirine can undergo thermal [4+2] cycloadditions with dienes to give an aziridine. Interestingly, the acyl substituent ends up *exo*, with the aziridine ring *endo*. This is thought to be due to the preference for the lone pair on the azirine nitrogen to be *exo* in the transition state, minimizing lone-pair π interactions.[125]

For example, Alves *et al.* reported that azirine **148** could undergo cycloaddition with cyclopentadiene to give the aziridine **149** (Scheme 1.44).[126-128]



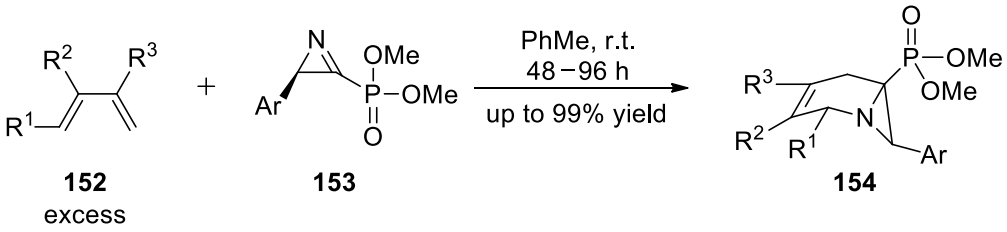
Scheme 1.44. Cycloaddition of azirine with diene.

However, in reactions where the diene is part of a furan ring, this selectivity is reversed.[128] The isomer with the aziridine ring *endo* is thought to be formed first, but retro Diels-Alder reaction and re-addition eventually gives aziridine **151** (Scheme 1.45).[128]



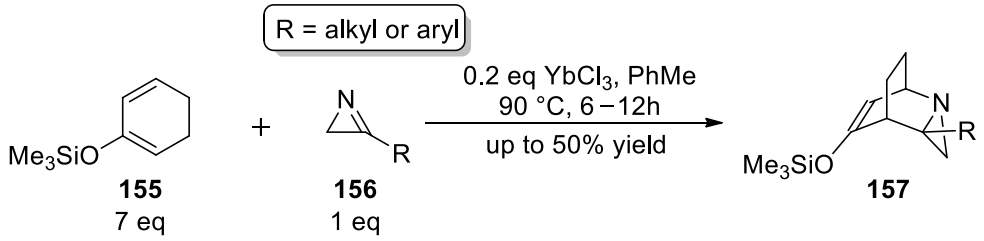
Scheme 1.45. Cycloaddition with furan.

Davis *et al.* reported that phosphonate substituted aziridine **154** could be produced stereospecifically starting from the chiral azirine **153** under thermal conditions.[129]



Scheme 1.46. Davis *et al.*'s synthesis of chiral phosphonate aziridine **154**.

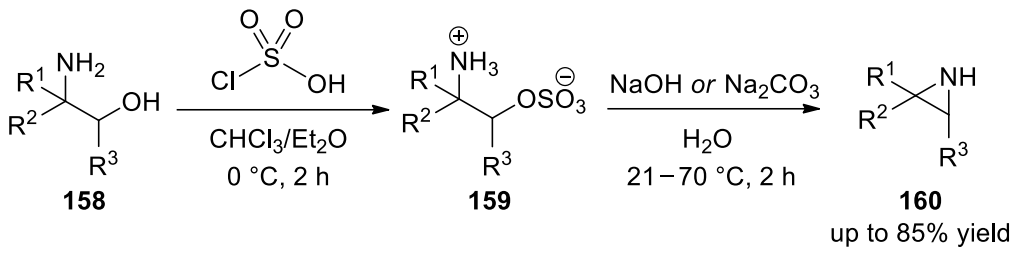
Lewis acid catalyst such as that $ZnCl_2$ or $YbCl_3$ can also be used to accelerate the cycloaddition of azirines with dienes.[130-133] This is useful in cases where the azirine does not have an activating carboxyl/phosphonyl group at the sp^2 carbon. For example, Somfai *et al.* reported that $YbCl_3$ catalysed the cycloaddition of diene **155** with 3-alkyl/aryl azirine **156** to give aziridine **157** (Scheme 1.47).[130-131]



Scheme 1.47. $YbCl_3$ catalysed cycloaddition of diene **155** with azirine **156**.

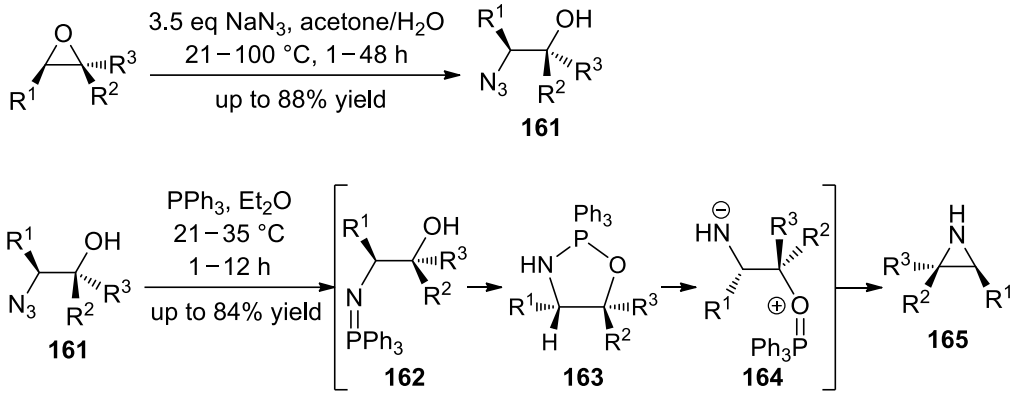
1.5.4 Ring closure of 1,2-amino derivatives

Ring closure of 1,2-amino derivatives is one of the oldest and most effective way to synthesize aziridines. Li *et al.* reported an adaptation of the Wenker synthesis to give various unprotected *N*H aziridines from the 1,2-amino alcohol (Scheme 1.48).[134] They first formed the sulfate **159** by reacting the 1,2-amino alcohol **158** with $ClSO_3H$, removed the solvent, then cyclized **159** to **160** by adding aq NaOH or aq Na_2CO_3. This is an improvement over the original Wenker synthesis which required extremely harsh conditions of 250 °C and concentrated H_2SO_4.[135]



Scheme 1.48. Li *et al.*'s modified Wenker synthesis of aziridines.

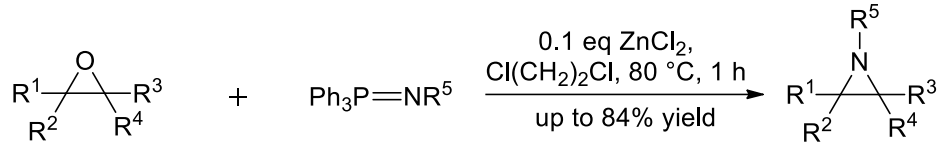
Starting from epoxides, it is also possible to synthesize aziridines by first ring opening the epoxide with a nitrogen nucleophile, before effecting ring closure to give the aziridine. Blum *et al.* first reported reacting an epoxide with sodium azide, followed by treatment of the 2-azido alcohol **161** with PPh_3, which gives aziridine **165** with loss of $O{=}PPh_3$ (Scheme 1.49).[136]



Scheme 1.49. Blum *et al.*'s conversion of epoxides to aziridines.

The mechanism is thought to proceed *via* intermediate **162**, which isomerizes to **163** and then **164**, before cyclization to give aziridine **165**.[137] If racemic epoxide is used, the reaction proceeds to give the aziridine with the same relative configuration as the epoxide, while if a chiral epoxide is used, the aziridine that is formed has the same relative configuration but with the opposite absolute configuration.[138]

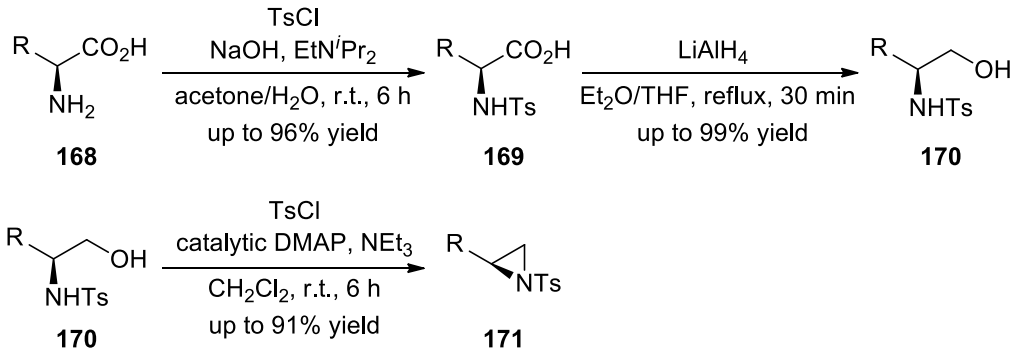
Other ring-openings of epoxides and subsequent ring closures to give aziridines have also been reported, but usually lead to aziridines that are *N*-protected. Jørgensen *et al.* reported a route similar to Blum *et al.*, using ZnI_2 catalysed addition of iminophosphoranes $Ph_3P{=}N$Ph or $Ph_3P{=}N^i$Pr to epoxides to give the *N*Ph or N^iPr aziridine in one step (Scheme 1.50).[139]



Scheme 1.50. Jørgensen *et al.*'s synthesis of aziridine from epoxide.

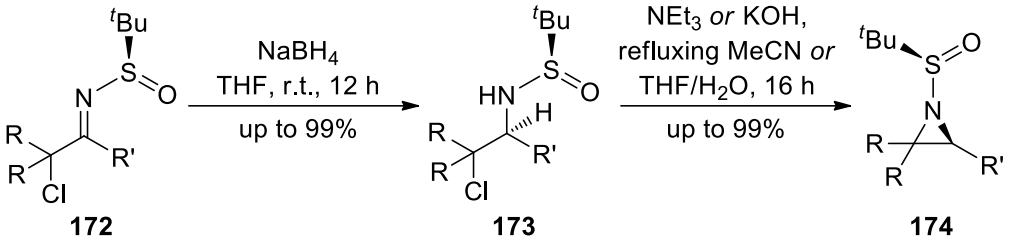
Other routes from epoxides to aziridine based on phosphorus[140] and sulfur[141] chemistry have been reported; all of them involve cyclization of a 1,2-amino intermediate to give the aziridine. Using hydrolytic kinetic resolution of racemic epoxides with chiral catalysts, it is also possible to synthesize chiral aziridines.[142]

Another way to make aziridines is by reduction of chiral amino acid derivatives, and cyclization of the 1,2-amino alcohol. Craig *et al.* reported that starting from chiral α-amino acid **168**, reduction of the *N*-tosyl acid **169** with $LiAlH_4$ gave the 1,2-amino alcohol derivative **170**, which was then cyclized to give *N*-Ts aziridine **171** (Scheme 1.51).[143] Other methods where the α-amino acid is first reduced before being tosylated have also been reported.[144]



Scheme 1.51. Craig *et al.*'s synthesis of *N*-Ts aziridines from α-amino acids.

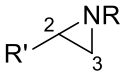
De Kimpe *et al.* reported that stereocontrolled reduction by $NaBH_4$ of α-chloro *N*-*tert*-butylsulfinyl imine **172** gives amine **173**, which can be cyclized to aziridine **174** in good yields using base (Scheme 1.52).[145]



Scheme 1.52. De Kimpe *et al.*'s synthesis of aziridine from imine **172**.

1.6 Ring opening of aziridines

The most common and useful reactions of aziridines are its ring openings.[1, 4-5] The ring opening of aziridines can be broadly classified into two categories: ring opening of activated aziridines, and ring opening of unactivated aziridines.[7] Activated aziridines have an electron withdrawing group on the aziridine nitrogen, such as **175a** – **d**, whereas unactivated aziridines have H (**175e**), alkyl (**175f**) or aryl (**175g**) substituents on the aziridine nitrogen (Figure 1.6). In the case of 2-substituted aziridines **175**, the regiochemical outcome of the ring opening can depend on whether the aziridine is activated or unactivated, the nucleophile used, as well as the reaction conditions.



175

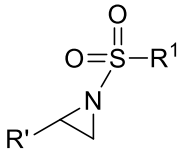
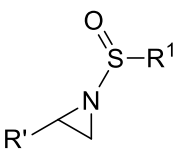
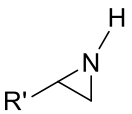
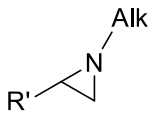
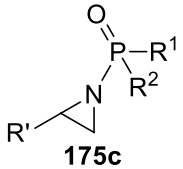
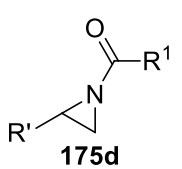
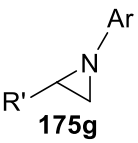
Activated aziridines have R = electron withdrawing groups on aziridine nitrogen, such as:	Unactivated aziridines have R = H, alkyl, or aryl groups on aziridine nitrogen, such as:
 **175a**  **175b**	 **175e**  **175f**
 **175c**  **175d**	 **175g**

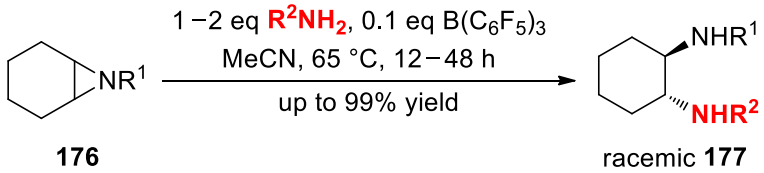
Figure 1.6. Activated and unactivated aziridines.

Generally, with activated aziridines **175a** – **d**, nucleophiles tend to attack at the less hindered 3-position of the aziridine; however, when the R' substituent at the 2 position of an activated aziridine **175a** – **d** is an aromatic group, attack at the 2 position can be favoured.[7] With unactivated aziridines **175e** – **g**, nucleophiles can attack at either the 2 or 3 position depending on the acid catalyst and nucleophile used.[7]

There exists a large amount of literature on the ring opening of both activated and unactivated aziridines with carbon, nitrogen, sulfur, and halide nucleophiles; for every aziridine synthesized, a multitude of different nucleophiles can be used to ring open them.[4] Here, we highlight pertinent examples.

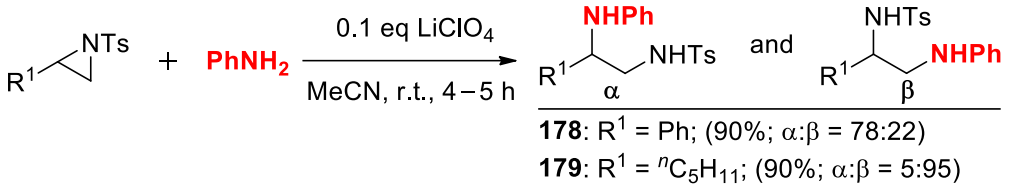
1.6.1 Ring opening of aziridines with nitrogen nucleophiles

Some primary amines are known to ring open aziridines in the absence of Lewis acids.[146] However, Lewis acids such as $BF_3{\cdot}OEt_2$, $BiCl_3$, $B(C_6F_5)_3$, $LiClO_4$, or $InBr_3$ are more commonly used to add amines to aziridines.[147-151] Yudin *et al.* reported that using $B(C_6F_5)_3$ as Lewis acid, symmetrical *N*-alkyl aziridine **176** could be ring opened by amines such as $BnNH_2$ and $PhNH_2$ (Scheme 1.53).[149] Similar results were reported by Singh *et al.* under solvent free conditions using silica gel.[152]



Scheme 1.53. Yudin *et al.*'s $B(C_6F_5)_3$ catalysed ring openings of aziridines with amines.

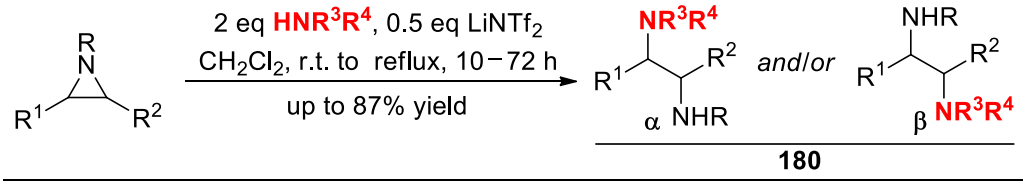
Using $LiClO_4$ as Lewis acid, Yadav *et al.* reported that *N*-tosyl aziridines could be ring opened by $ArNH_2$ giving 1,2-diamines.[150] However, in cases of non-symmetrical aziridines, regioselectivity was not complete (Scheme 1.54). With R^1 = aromatic, the amine attacked mostly at the benzylic position, but when R^1 = alkyl, attack was mostly seen at the less hindered position.



Scheme 1.54. $LiClO_4$ catalysed ring openings of aziridines with amines.

This preference for nucleophiles to attack at the less hindered end of 2-alkyl substituted activated aziridines, and at the benzylic position for 2-aromatic activated aziridines has been observed in a number of other reports.[7, 151, 153]

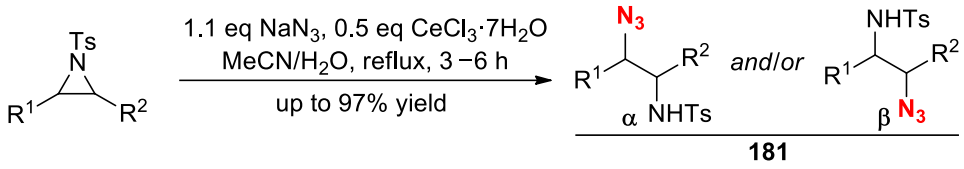
A safer alternative to using $LiClO_4$ is $LiNTf_2$. Cossy *et al.* reported that $LiNTf_2$ is an extremely efficient Lewis acid for the ring opening of *N*-tosyl, *N*-Boc and *N*-alkyl aziridines with primary and secondary amines (Scheme 1.55).[154]



Scheme 1.55. Cossy *et al.*'s $LiNTf_2$ catalysed aziridine ring openings.

The ring opening of aziridines with azides is usually done with either NaN_3 or Me_3SiN_3. In the absence of any Lewis acid, NaN_3 is known to ring open activated *N*-tosyl aziridines in $MeCN/H_2O$ with good yields quickly; however, the corresponding reaction with unactivated *N*-aryl aziridines is very sluggish with lower yields obtained.[155]

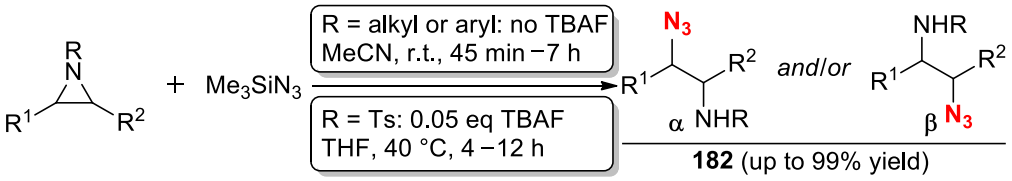
More commonly, reactions of aziridines with NaN_3 are effected in the presence of Lewis acids such as $Ce^{IV}(NH_4)_2(NO_3)_6$ (Ceric ammonium nitrate, CAN), $CeCl_3{\cdot}7H_2O$, $LiClO_4$ or $AlCl_3$.[156-159] For example, Yadav *et al.* reported that $CeCl_3{\cdot}7H_2O$ was an extremely effective catalyst in the regioselective ring opening of *N*-tosyl aziridines with NaN_3, giving product **181** (Scheme 1.56).[157]



181

Scheme 1.56. $CeCl_3{\cdot}7H_2O$ catalysed ring openings of aziridines with NaN_3.

Me_3SiN_3 can also be used to ring open aziridines with azide (Scheme 1.57). Unactivated *N*-alkyl and *N*-aryl aziridines can be ring opened with Me_3SiN_3 in the absence[160] of any external catalyst with good regioselectivity, but activated *N*-tosyl aziridines required $^nBu_4NF$ as catalyst.[161] Good yields were obtained in both cases.



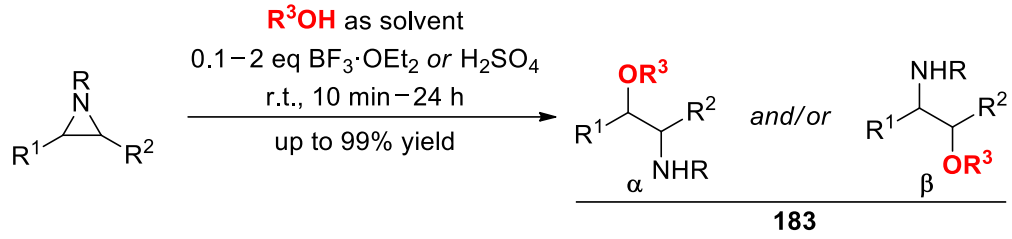
182 (up to 99% yield)

Scheme 1.57. Ring openings of aziridines with Me_3SiN_3.

1.6.2 Ring opening of aziridines with oxygen nucleophiles

The ring opening of both activated and unactivated aziridines by alcohols is often done by using the alcohol as a solvent, with an appropriate Lewis acid, such as $Ce^{IV}(NH_4)_2(NO_3)_6$, $Sn(OTf)_2$ or $BF_3{\cdot}OEt_2$.[156, 162] Brønsted acids dissolved in the alcohol can also be used,[163] and in the case of H_2O as nucleophile, ring opening of activated aziridines can be achieved in the absence of any external Brønsted acid catalyst at elevated temperatures.[164]

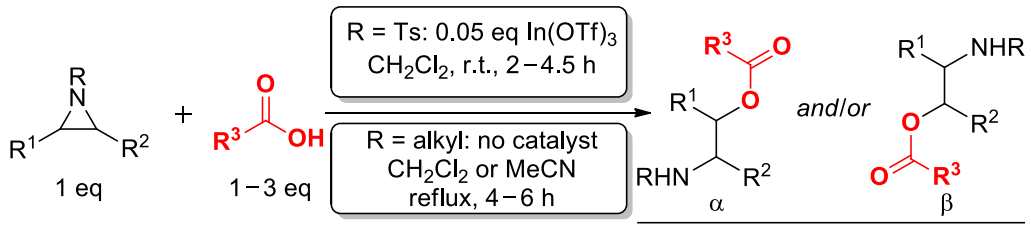
For example, Singh *et al.*[162] and Uneyama *et al.*[163] respectively reported that $BF_3{\cdot}OEt_2$ and H_2SO_4 catalyse the ring opening of *N*-alkyl, *N*-aryl and *N*-tosyl aziridines by alcohols (Scheme 1.58).



183

Scheme 1.58. Ring openings of aziridines with ROH.

Carboxylic acids can also ring open aziridines. *N*-Tosyl aziridines are ring opened by carboxylic acids using $In(OTf)_3$ as Lewis acid catalyst,[165] but unactivated *N*-alkyl aziridines react with carboxylic acids without the need for any external Lewis acid (Scheme 1.59).[166-167]

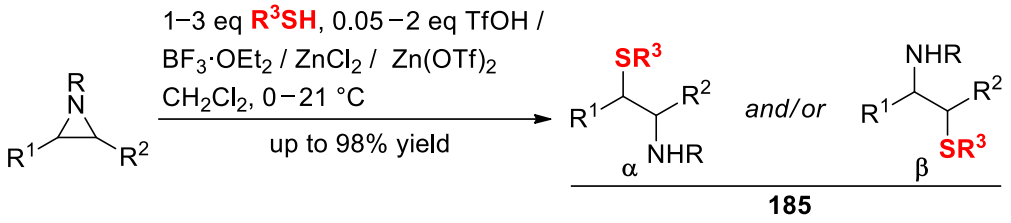


184 (up to 95% yield)

Scheme 1.59. Ring openings of aziridines with carboxylic acids.

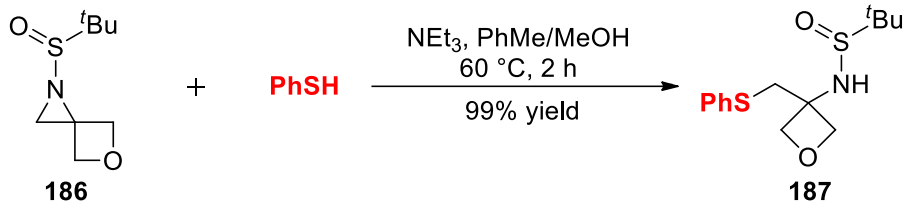
1.6.3 Ring opening of aziridines with sulfur nucleophiles

Thiols are sufficiently nucleophilic that they can ring open some aziridines in the absence of any acidic or basic catalyst.[168] More commonly however, either Lewis or Brønsted acids are used to accelerate the ring opening of aziridines by thiols. Brønsted acids such as TfOH, and Lewis acids such as $BF_3{\cdot}OEt_2$, $ZnCl_2$ and $Zn(OTf)_2$ have been reported to catalyse the ring opening of *N*-alkyl, *N*-Boc and *N*-tosyl aziridines (Scheme 1.60).[169-172]



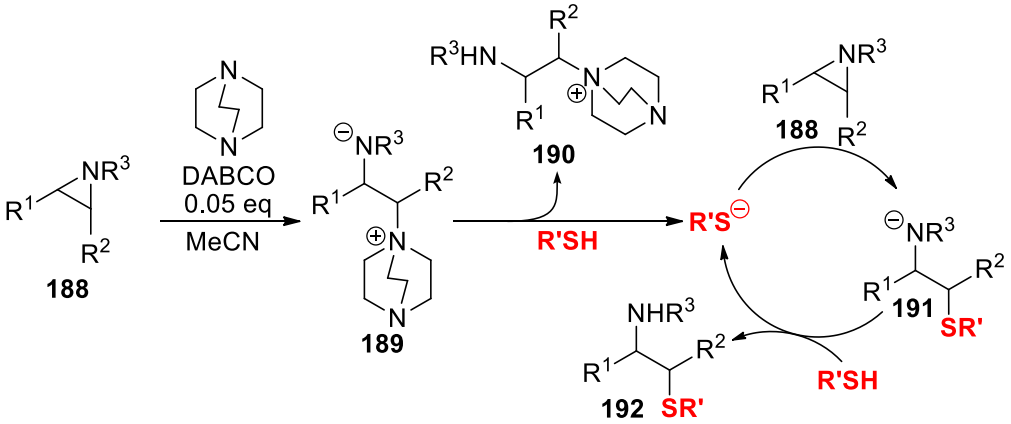
Scheme 1.60. Literature ring openings of aziridines with thiols.

Aziridines can also be ring opened by thiols in the presence of bases such as NEt_3.[173-174] Hamzik *et al.* reported that *N*-sulfinyl aziridine **186** was ring opened by thiophenol to give **187** as the only regioisomer (Scheme 1.61).[174]



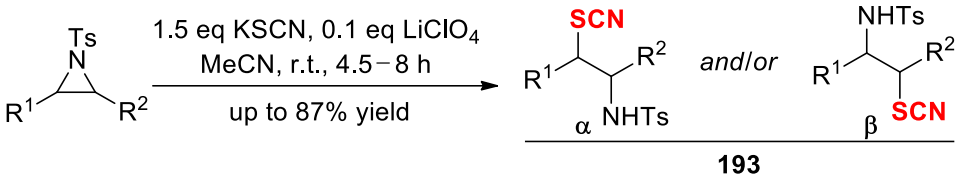
Scheme 1.61. NEt_3 catalysed ring opening of aziridine **186**.

Wu *et al.* reported that the tertiary amine DABCO was able to catalyse the ring opening of *N*-tosyl and *N*-benzyl aziridine **188** by thiols by acting as a nucleophilic "trigger" to produce intermediate **189**, which was able to act as a base, eventually giving the ring opened product **192** (Scheme 1.62).[175] Hou *et al.* reported that $^{n}Bu_3P$ was also able to promote this reaction.[176]



Scheme 1.62. Wu *et al.*'s DABCO catalysed ring openings of aziridines.

Thiocyanate (NCS^-) can also ring open aziridines. Yadav *et al.* reported KSCN ring opened *N*-tosyl aziridines in the presence of $LiClO_4$ as Lewis acid, giving **193** after aqueous work-up (Scheme 1.63).[177]

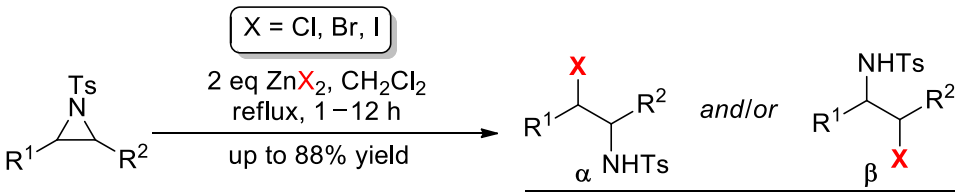


193

Scheme 1.63. Yadav *et al.*'s ring openings of *N*-tosyl aziridines with KSCN.

1.6.4 Ring opening of aziridines with halides

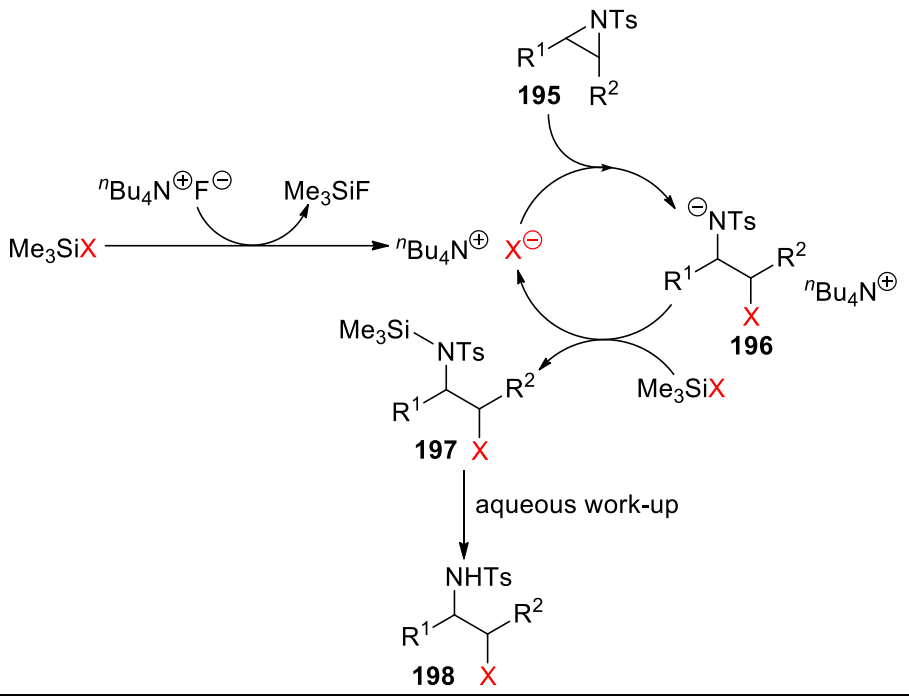
Aziridines can be ring opened by chloride, bromide and iodide anions using metal halide salts, hydrogen halides, or trimethylsilyl halides. Various metal halides have been reported to ring open activated aziridines, such as $MgBr_2$, $InCl_3$, $InBr_3$, InI_3, LiCl, LiBr, LiI.[178-182] However, the most general method appears to be use of zinc(II) halides $ZnCl_2$, $ZnBr_2$ and ZnI_2, which give excellent regioselectivity with *N*-tosyl aziridines bearing an aromatic substituent (Scheme 1.64).[181]



194

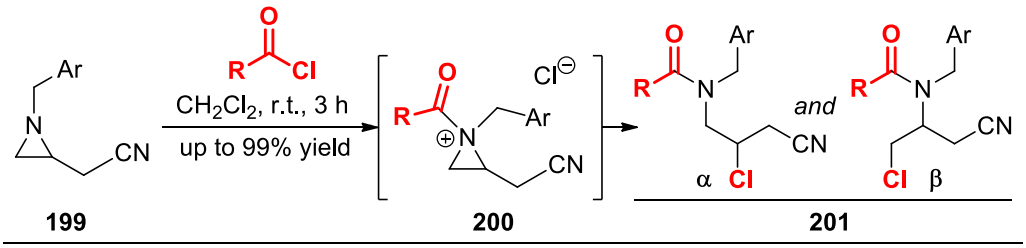
Scheme 1.64. Ring openings of *N*-tosyl aziridines with zinc(II) halides.

Me_3SiCl, Me_3SiBr and Me_3SiI can ring open activated aziridines in the presence of a suitable Lewis base catalyst such as F^- or TMEDA.[161, 183-184] These authors proposed that the Lewis base first reacts with the trimethylsilyl halide to give the halide anion; the initially formed *N*-silyl **197** is hydrolysed upon aqueous work-up to give **198** (Scheme 1.65).[161]



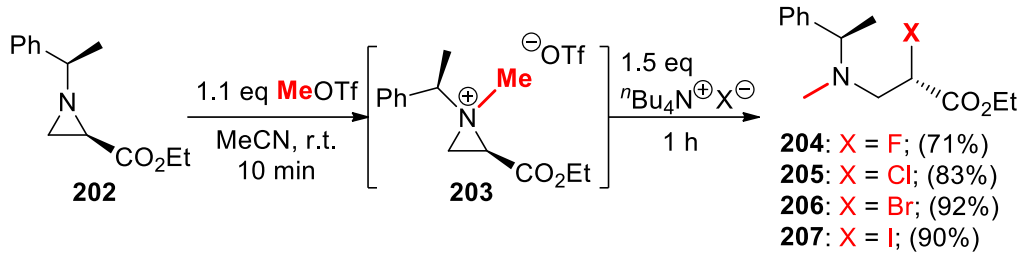
Scheme 1.65. Wu *et al.*'s proposed catalytic cycle.

Unactivated aziridines can be ring opened by halides by first converting them to the aziridinium cation, which then undergoes attack by the halide anion. De Kimpe *et al.* reported that unactivated aziridine **199** was ring opened by various acyl chlorides to give **201** (Scheme 1.66).[185]



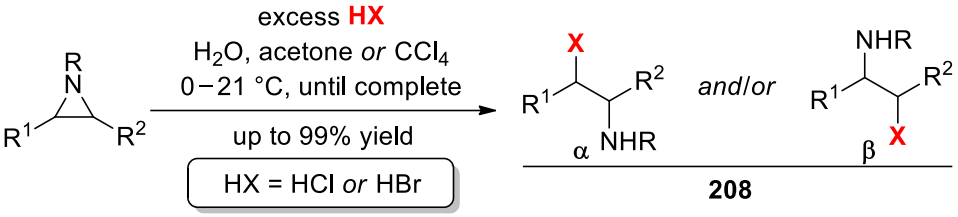
Scheme 1.66. De Kimpe *et al.*'s acylation and ring openings of aziridines.

Alternatively, De Kimpe *et al.* reported that by methylating *N*-alkyl aziridine **202**, the aziridinium triflate salt **203** could be ring opened by various tetra-butyl ammonium halides including fluoride with almost complete stereo and regioselectivity (Scheme 1.67).[186] Attack of halide was at the more substituted end as the reaction was under thermodynamic control.



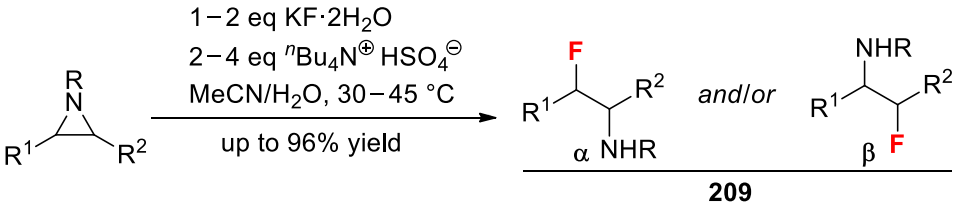
Scheme 1.67. De Kimpe *et al.*'s methylation and ring openings of aziridines.

Another way to ring open aziridines with halide anions is to react the aziridine directly with the hydrogen halide.[163, 187-188] However, this usually works only for HCl and HBr (Scheme 1.68).



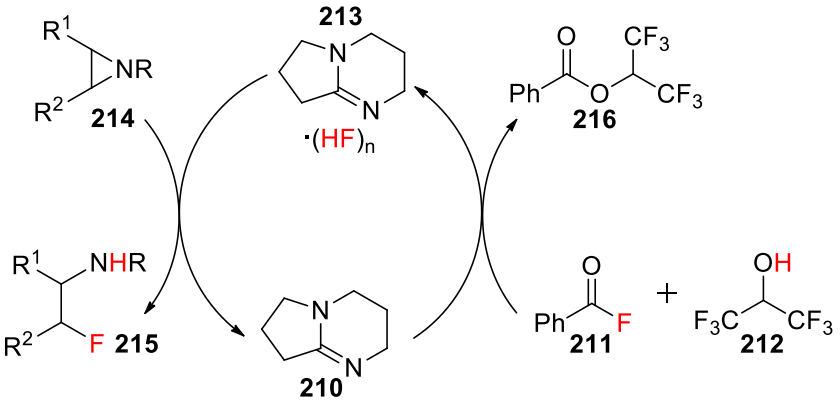
Scheme 1.68. Ring openings of aziridines with HCl or HBr.

There are very few reports on ring openings of aziridines by fluoride due to the low nucleophilicity of F^-. While HF can ring open aziridines, this method is not very popular because it is highly corrosive and can react with glass.[189] Some metal fluoride salts such as $KF{\cdot}2H_2O$ and NiF_2 also ring open aziridines.[190-191] Fan *et al.* reported that $KF{\cdot}2H_2O$ ring opens *N*-tosyl, *N*-aryl and *N*-alkyl aziridines in the presence of $^nBu_4NHSO_4$ to give **209**, although the role $^nBu_4NHSO_4$ of was not explained (Scheme1.69).[190] Zhang *et al.* reported that partially hydrated NiF_2 could effect the same transformation.[191]



Scheme 1.69. Zhang *et al.*'s ring openings of aziridines with $KF{\cdot}2H_2O$.

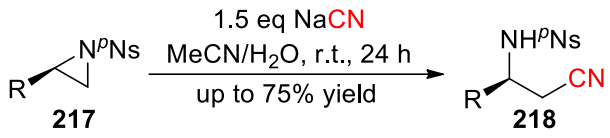
Doyle *et al.* reported an interesting Lewis base catalysed *in situ* generation of amine-HF reagents which can ring open activated and unactivated aziridines (Scheme 1.70).[192] Using 1,5-diazabicyclo[4.3.0]non-5-ene (**210**), benzoyl fluoride (**211**) and hexafluoroisopropanol (**212**), the amine-HF complex **213** was formed, which could ring open aziridine **214** to give **215**.



Scheme 1.70. Doyle *et al.*'s *in situ* generation of amine-HF complex **213**.

1.6.5 Ring opening of aziridines with carbon nucleophiles

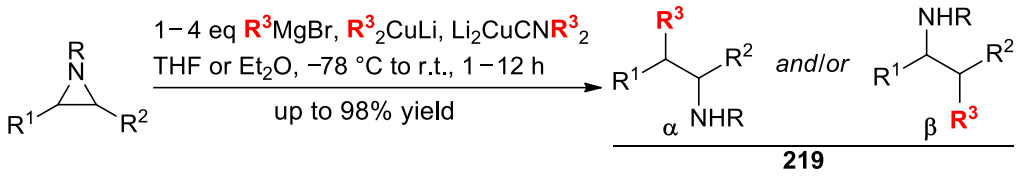
The simplest carbon nucleophile, the cyanide anion can ring open aziridines. If the aziridine is sufficiently activated, as in *N*-nosyl aziridines, CN^- is sufficiently nucleophilic to attack the aziridine in the absence of any external Lewis acids. Farràs *et al.* reported that starting from chiral 2-alkyl, *N*-^{p}Ns aziridine **217**, attack of NaCN from the less hindered carbon gave **218** as a single stereo and regioisomer (Scheme 1.71).[193]



Scheme 1.71. Farràs *et al.*'s ring opening of aziridine **217** with NaCN.

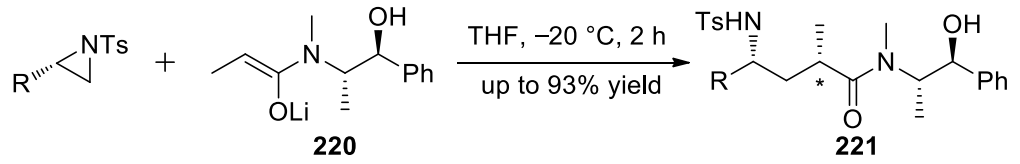
However, with less activated *N*-tosyl aziridines, a Lewis acid such as $LiClO_4$ is needed.[158] Alternatively, Me_3SiCN can be used to ring open *N*-tosyl aziridines with $^nBu_4NF$ as catalyst.[161]

Organometallic reagents can be used to ring open aziridines. While unactivated *N*-alkyl aziridines can be ring opened by organometallic reagents, this method is not very popular.[194-195] More commonly, organometallic reagents are used to ring open activated *N*-sulfonyl, *N*-sulfinyl and *N*-phosphonate aziridines (Scheme 1.72).[174, 196-199] The carbanion usually attacks the less hindered carbon with high regioselectivity, except with 2-aryl substituted activated aziridines.[197]



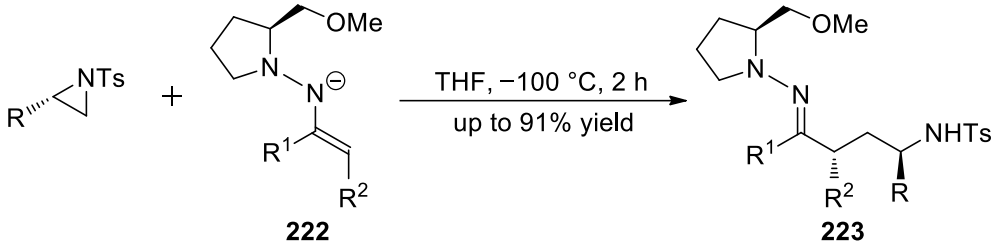
Scheme 1.72. Literature ring openings of aziridines with organometallic reagents.

Enolates and enolate equivalents have also been reported to ring open aziridines through carbon. Vicaro *et al.* showed that chiral enolate **220** ring opens various *N*-tosyl aziridines at the less hindered carbon with high diastereoselectivity to give **221** (Scheme 1.73).[200] Interestingly, high regioselectivity was also observed even when there was a phenyl group at the 2-position of the aziridine.



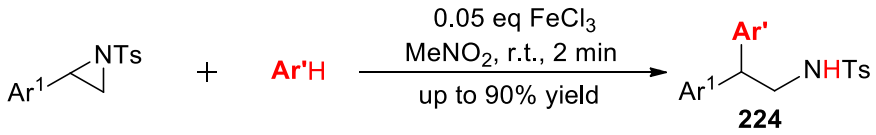
Scheme 1.73. Vicario *et al.*'s ring openings of aziridines with enolate **220**.

Enders *et al.* reported ring openings of unsubstituted and 2-benzyl *N*-tosyl aziridines with SAMP hydrazone anion **222** to give **223** (Scheme 1.74).[201]



Scheme 1.74. Enders *et al.*'s ring openings with SAMP hydrazone anion **222**.

Arenes and heteroaromatics can also ring open *N*-sulfonyl aziridines in the presence of a suitable Lewis acid, such as $AlCl_3$, $AuCl_3$, $InCl_3$, $In(OTf)_3$, $AgPF_6$, or $FeCl_3$.[202-207] Most of these examples involved the ring opening of *C*-aryl, *N*-tosyl aziridines, such as that reported by Wu *et al.* with $FeCl_3$ (Scheme 1.75).[207]



Scheme 1.75. Wu *et al.*'s ring openings of aziridines with arenes.

Chapter 2:

Flow Synthesis and Openings of Aziridines from 1,2-Amino Alcohols

2.1 Introduction to flow chemistry

There have been a number of excellent reviews written on flow chemistry.[208-214] This short introduction does not aim to replicate these reports but to provide a brief summary on the principles of flow chemistry.

Currently, the majority of synthetic organic chemistry in research and development settings is carried out in batch reactors, conventionally in a round bottom flask. However, a major problem faced by synthetic organic chemists is successful scaling up of reactions from laboratory conditions to mass production.[208] One way to avoid the need to optimize reaction conditions each time a batch reaction is run on a bigger scale is to use flow chemistry.[212] Flow chemistry is the continuous synthesis of chemicals in channels, tubes or pipes. Rather than ***scaling up*** a batch reaction by conducting the reaction on a larger scale in a bigger flask, flow chemistry aims to increase production by ***scaling out***: the reaction is run under the same conditions, but in multiple parallel flow reactor systems.[213]

Not having to optimize the conditions for chemical reactions at different scales is an attractive proposition in industrial processes.[208] Thus, there has been growing interest in recent years in carrying out chemical reactions under continuous flow conditions. Furthermore, there are other inherent advantages to running a reaction using continuous flow methodology, which will be described later.

2.1.1 Types of flow reactors

Flow reactors can be fabricated from various substrates such as glass, silicon, metal or polymers, with the exact substrate used dependent on chemical compatibility or cost.[214] Flow reactors can be classed into two main categories: microfluidic flow reactors have reaction channels that are less than 500 μm; mesofluidic flow reactors have reaction channels larger than 500 μm but smaller than 3 mm.[213] Microfluidic flow reactors have a larger surface area to volume ratio, and thus have better heat transfer characteristics, making microfluidic flow reactors better for exothermic reactions.[211]

However, the smaller channel diameter of microfluidic flow reactors makes them much more prone to blockages. Mesofluidic flow reactors are less prone to blockages, and are thus more versatile for chemical reactions that are not highly exothermic.

2.1.2 Mixing of reactants in a flow reactor

In a batch reaction in a round bottom flask, mixing of two different miscible solutions is achieved by using a magnetic stirrer to effect mechanical agitation. In a flow reactor combining two reagent streams, mechanical agitation is not usually possible.[212] The Reynolds number (*Re*) is a dimensionless number used to quantify the ratio between inertial and viscous forces within a stream of fluid.[213] In a uniform tube, it is described by the equation:

$$Re = \frac{\text{inertial forces}}{\text{viscous forces}} = \frac{\rho d v}{\mu}$$

where ρ is density in kgm^{-3}, d is the diameter of the channel in m, v is the fluid velocity in ms^{-1}, and μ the dynamic viscosity in Nsm^{-2}. Fluid flow in microfluidic and mesofluidic flow reactors is characterized by low Reynolds numbers (usually below 250), which means that fluid flow is laminar, not turbulent.[213]

An approximation[212] for the time taken for reactants to diffuse in the channel of a flow reactor is given by Fick's law of diffusion:

$$t_d = \frac{L^2}{D}$$

where t_d is the diffusion time in s, L is the diffusion distance in m, and D is the diffusion coefficient in m^2s^{-1}. A consequence of Fick's law and low Reynolds numbers in most flow reactors means that after a T-junction combining two reagent streams, complete mixing by only diffusion is usually not fast enough.

Thus, rapid mixing is usually achieved by incorporation of a separate mixing unit after the T-junction of the flow reactor (the T-junction and the mixing unit is together refered to as the T-mixer), which combines the two reagent streams together. This can work by splitting the two reagent streams into many different 'laminae' and recombining them, or by inducing turbulence in a small section of the flow reactor so that the two reagent streams are completely mixed.[212]

2.1.3 Movement of fluid in a flow reactor

Movement of fluids in a flow reactor is usually achieved using a mechanical pump, such as syringe pumps, or HPLC pumps. This is usually the most expensive part of a flow reactor. Non-mechanical pumping has also been used in flow reactors, such as electro-osmotic flow pumping, which is achieved by using an electric field to move various polar solvents such as water, methanol or acetonitrile; however, this method is not very versatile and the highest flow rate that can be achieved is around 5 μLmin^{-1}.[213]

How fast the reagents flow through the flow reactor of a given volume before heating is stopped or the reaction quenched affects the residence time, which corresponds to how long a reaction takes to occur under batch conditions. A brief schematic of the various variables in a flow reactor is given in Figure 2.1.

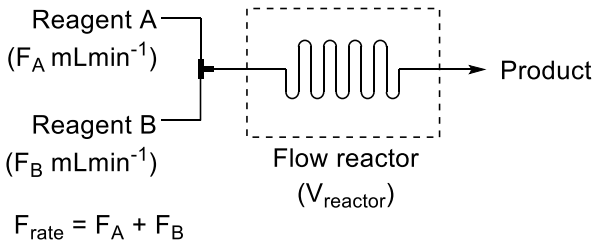


Figure 2.1. Schematic showing the various variables in a flow reactor.

The residence time, R_t (in min), is calculated by dividing the reactor volume, $V_{reactor}$ (in mL), by the total flow rate, F_{rate} (in mLmin^{-1}):

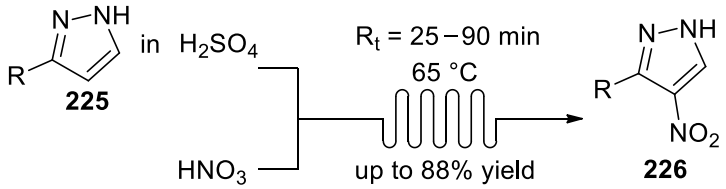
$$R_t = \frac{V_{reactor}}{F_{rate}}$$

2.1.4 Advantages of reactions in a flow reactor

Running a reaction under continuous flow methodology in a flow reactor can give a number of direct benefits, which will be described with examples in this section.

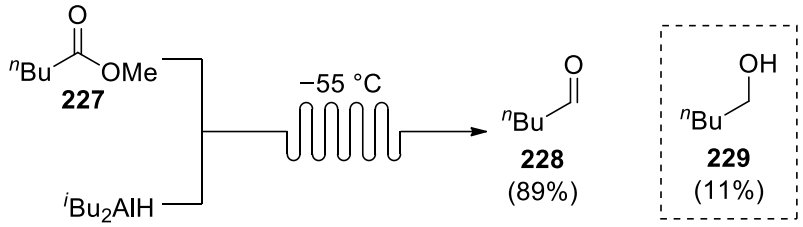
2.1.4.1 Better heat control

Running a reaction in a microfluidic or mesofluidic flow reactor can offer a better heat dissipation rate of around 5000 – 25 000 $Wm^{-2}K^{-1}$, compared to a rate of around 2000 $Wm^{-2}K^{-1}$ under batch conditions.[215] This can be extremely important in reactions that involve high exotherms, for both safety and product degradation reasons. For example, Pelleter *et al.* reported that the highly exothermic nitration of 3-alkylpyrazole **225** could be effected much more safely using continuous flow methodology (Scheme 2.1).[215] This is important as local hot spots can cause explosive decomposition of the nitrated products **226**, as well as causing unwanted side products.



Scheme 2.1. Pelleter *et al.*'s nitration of 3-alkylpyrazole **225** in flow.

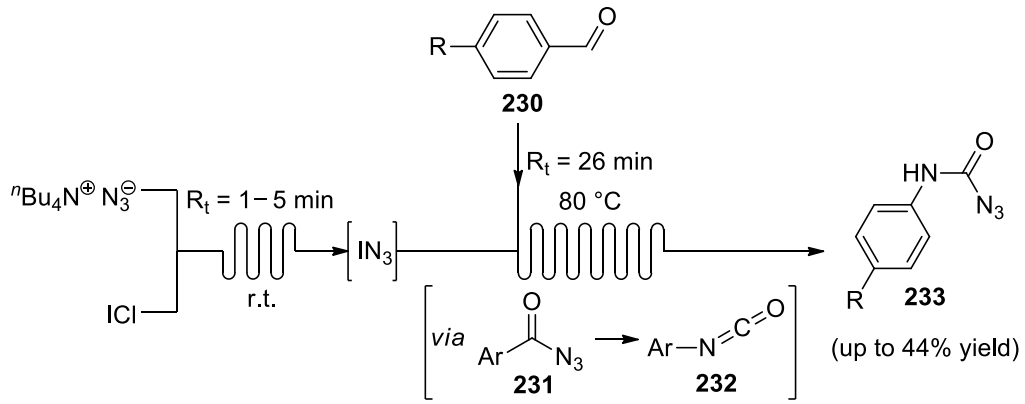
Better heat control can also improve the selectivity of products formed in a reaction. Roberge *et al.* reported that the DIBAL-H reduction of methylbutyrate (**227**) into butyraldehyde (**228**) could be effected with much higher selectivity against butyl alcohol (**229**) (89% aldehyde, only 11% alcohol) under continuous flow methodology at −55 °C (Scheme 2.2).[216] The batch process at the same temperature gave 63% aldehyde with 27% alcohol.



Scheme 2.2. Roberge *et al.*'s reduction with DIBAL-H in flow.

2.1.4.2 *In situ* generation of reactive or hazardous intermediates

Running a reaction under continuous flow methodology can allow small quantities of highly reactive or hazardous intermediates to be generated *in situ*. This can be important for safety considerations, or avoiding the need to isolate a reactive intermediate which is prone to decomposition. Wirth *et al.* reported that highly reactive iodine azide (IN_3) could be safely generated *in situ* from *n*butylammonium azide and iodine-chloride. IN_3 reacts with aldehyde **230** *via* a radical process to give acyl azide **231** which undergoes a Curtius rearrangement to give the isocyanate **232**. **232** then reacts with excess azide to give the final product **233** (Scheme 2.3).[217]



Scheme 2.3. Wirth *et al.*'s *in situ* generation of reactive IN_3.

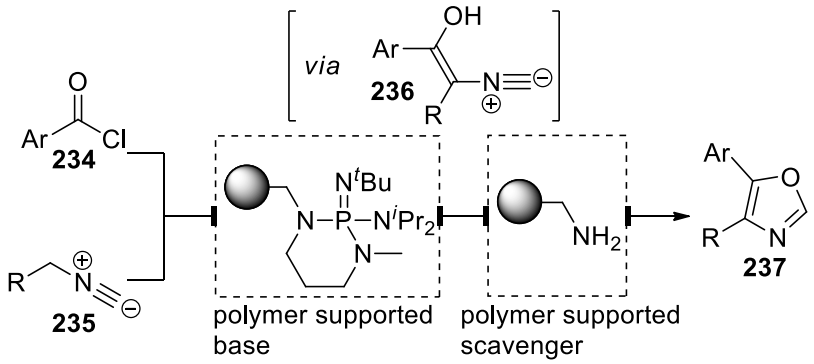
2.1.4.3 Rapid reactions at elevated temperatures and pressures

Certain chemical reactions benefit from faster rates at elevated temperatures, but are limited by the boiling point of the solvent used. With the right flow reactor, reactions can be run under continuous flow methodology above the boiling point of the solvent at elevated pressures; this can speed up the rate of reaction.[218] While running reactions in batch at high temperature and pressure is possible, elevated temperatures and pressures in a flow reactor are considered safer due to the lack of headspace in a flow reactor.

2.1.4.4 Immobilized reagents reduce the need for purification

The use of solid or polymer-supported reagents or catalysts can be combined with continuous flow methodology.[219] By flowing a dissolved reactant in a solvent through the supported reagent or catalyst, the outlet would give a stream of product with lesser need for purification to remove the remaining reagent or catalyst. Supported scavengers can also be used to remove any remaining starting materials.

Ley *et al.* has pioneered continuous flow methodology involving solid and polymer-supported reagents. In one example, polymer-supported base was used to induce cyclization of acyl chloride **234** and isocyanate **235** to give 4,5-disubstituted oxazoles **237** (Scheme 2.4).[220] A polymer supported scavenger was also used to remove unreacted starting material.



Scheme 2.4. Ley *et al.*'s use of supported reagents and scavengers.

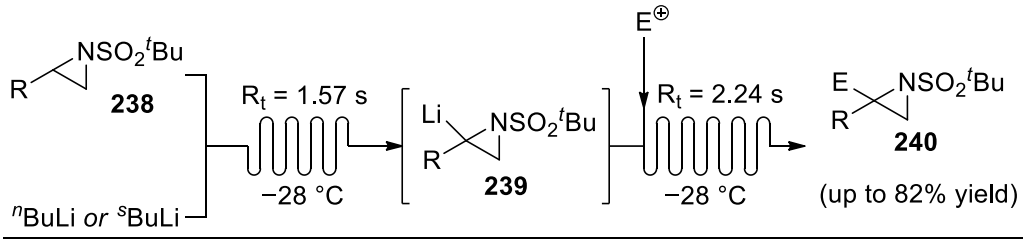
2.1.5 Disadvantages of running reactions in flow

It should be pointed out running a reaction using continuous flow methodology has a number of disadvantages as well. Many chemical reactions which produce insoluble precipitates and by-products are unsuitable for flow methodology as this can clog up a flow reactor and cause blockages.[213] Furthermore, chemistry run under continuous flow methodology should ideally involve homogenous solutions; while there have been examples of flow chemistry involving multiple phases such as gas and liquid, or biphasic mixtures, non-homogenous conditions in flow require special equipment.

2.1.6 Flow chemistry of aziridines

At the outset of my PhD studies in 2013, a literature search on aziridines in flow chemistry only yielded three papers. This included a single report on the synthesis of aziridines, and none on the ring opening reactions of aziridines

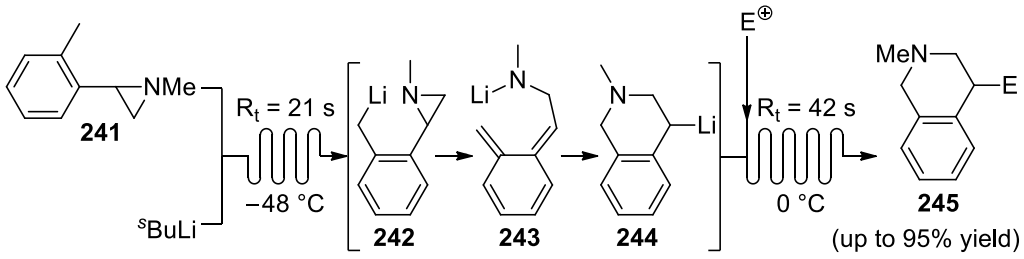
Nagaki *et al.* generated *N*-(*t*-butylsulfonyl)aziridinyllithium **239** from *N*-(*t*-butyl sulfonyl)aziridine **238** and ^{n}BuLi or ^{s}BuLi in a microreactor, and subsequently reacted **239** with electrophiles in a telescoped process (Scheme 2.5).[221]



Scheme 2.5. Nagaki *et al.*'s generation and reactions of aziridinyllithiums in flow.

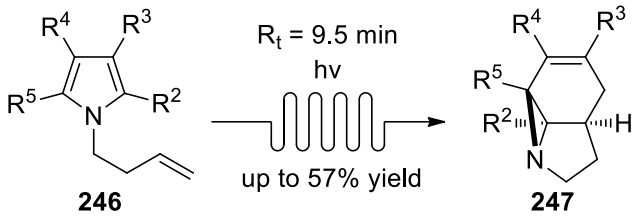
Nagaki *et al.* reported that the use of a microreactor allowed the effective generation of these reactive organolithiums at a higher temperature of −28 °C, compared to the much lower temperature of −78 °C needed for the batch reaction.

Nagaki *et al.* further expanded on this flow chemistry.[222] Aziridine **241** was deprotonated by ^{s}BuLi to give the organolithium **242**, which isomerized via **243** to give the nucleophile **244**. **244** was subsequently reacted with various electrophiles in a telescoped process to give 1,2,3,4-tetrahydroisoquinolines **245** in overall moderate to good yields (Scheme 2.6).



Scheme 2.6. Nagaki *et al.*'s in flow synthesis of 1,2,3,4-tetrahydroisoquinolines.

In 2013, the only report on the synthesis of aziridines in flow was that by Booker-Milburn *et al.*, in which they effected the photocycloaddition/rearrangement of pyrrole **246** to give aziridine **247** (Scheme 2.7).[223] Whilst an impressive rearrangement, this method is not a general route to aziridines, and is limited to *N*-functionalized pyrroles.

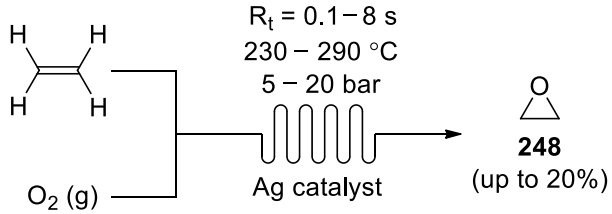


Scheme 2.7. Booker-Milburn *et al.*'s in flow synthesis of aziridines.

One of the many advantages continuous flow methodology has over batch process is that flow chemistry can be used to generate and handle hazardous and reactive reagents in a safe way. Other than the literature just explored, there were no other reports on aziridines in flow. We were thus interested to investigate if continuous flow methodology could be applied to the synthesis of aziridines and their ring openings, and if these two processes could be combined. This would be attractive to industry, as a concern in the large scale manufacture of aziridines is its potential toxicity; avoiding the need to isolate an aziridine intermediate by directly reacting it in flow would be ideal.

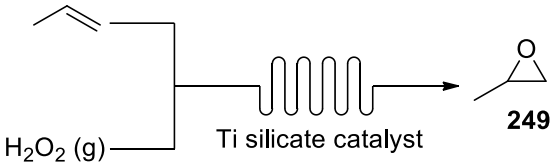
2.1.7 Related research on epoxides in flow chemistry

Closely related to aziridines are epoxides. The synthesis and ring openings of epoxides under continuous flow methodology had received more attention at the time my PhD began. Schüth *et al.* reported in 2002 the gas phase oxidation of ethene by oxygen using silver catalysis to give ethylene oxide (**248**) using a specially constructed microreactor (Scheme 2.8).[224]



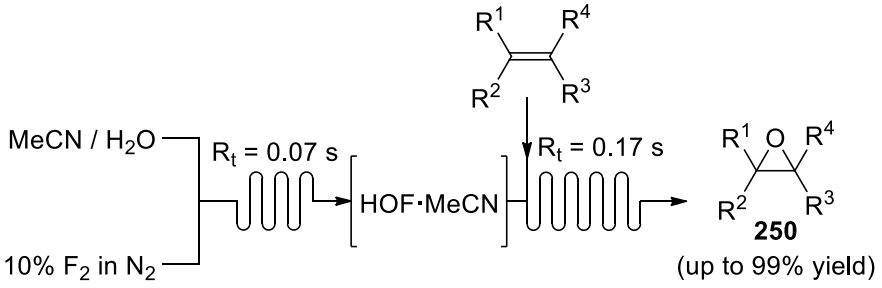
Scheme 2.8. Schüth *et al.*'s oxidation of ethene with oxygen.

Markowz *et al.* reported a similar gas phase oxidation of propene with H_2O_2 in a microreactor (Scheme 2.9), but the reaction conditions and yields were not disclosed; their results were used for scale up to pilot scale.[225]



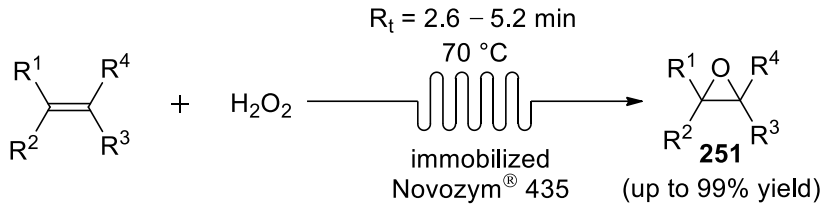
Scheme 2.9. Markowz *et al.*'s oxidation of propene with H_2O_2.

McPake *et al.* epoxidized a range of alkenes in a continuous flow reactor in 2009.[226] HOF·MeCN was generated *in situ*, which was used to epoxidize various alkenes (Scheme 2.10). The advantage of this method was that the highly oxidizing and corrosive HOF·MeCN did not need to be isolated, and could be used immediately.



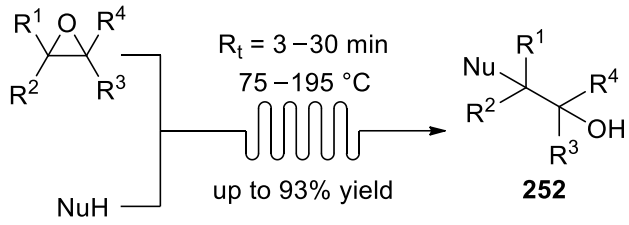
Scheme 2.10. McPake *et al.*'s epoxidation of alkenes with HOF·MeCN.

In 2009, Wiles *et al.* effected the epoxidation of a variety of alkenes using H_2O_2 by an immobilized enzyme, Novozym® 435 (Scheme 2.11).[227] It is thought that the enzyme catalyzes the formation of peracetic acid from hydrolysis of the EtOAc solvent which then epoxidizes the alkene. Wiles *et al.* reported the advantage of carrying out the chemo-enzymatic epoxidation of alkenes under continuous flow compared to in batch was that reaction times were reduced.



Scheme 2.11. Wiles *et al.*'s enzyme catalysed epoxidation of alkenes.

Munirathinam *et al.*[228] and Bedore *et al.*[229] managed to effect the ring opening of epoxides using continuous flow methodology, using sodium azide and various amines respectively (Scheme 2.12). Bedore *et al.* reported that by using a microreactor, higher temperatures above the boiling point of the solvent and/or amines could be reached, allowing faster reaction.



Scheme 2.12. Literature ring openings of epoxides under continuous flow.

2.2 Research hypothesis and aims

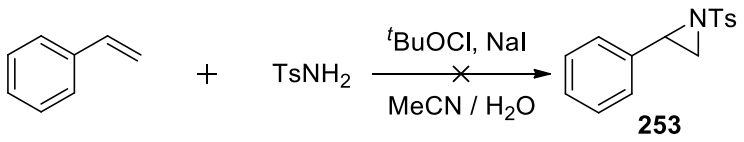
Based on the successes achieved with epoxides, and the importance of aziridines in synthesis,[1] we felt that it would be of interest to develop flow methods for the generation and ring opening reactions of aziridines. The application of continuous flow methodology with aziridines would potentially have a number of benefits, such as improved safety and faster reaction times.[208-213] Furthermore, we hoped to couple the synthesis of aziridines with subsequent cascade ring openings. This would allow the opportunity to make libraries of compounds by systematic variation of the starting materials used.[230]

2.3 Initial attempts to synthesize aziridines from alkenes

Our initial goal was the continuous flow synthesis of *N*-sulfonyl 2-phenylaziridines. These molecules are sufficiently activated towards ring opening by nucleophiles that they are useful intermediates, but are also stable enough to be isolated, characterized, and stored for long periods of time. The phenyl group increases the rate of nucleophilic attack as well as improves regioselectivity due to a S_N1/loose S_N2 transition state.[231-232]

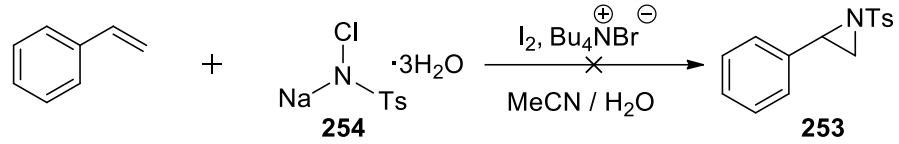
Initially, we explored the aziridination of styrene. The eventual goal was to adapt the procedure to a wider range of alkene substrates. The direct aziridination of alkenes is well studied, and offers the most attractive way of making aziridines due to the wide variety of alkenes that are commercially available and its directness.

One of the most important considerations when adapting batch processes for use under continuous flow methodology is solubility. This is to avoid blocking the channels of the microreactor. The solutions should be homogeneous as biphasic mixtures are not normally suitable for continuous flow methodology. In the context of alkene aziridinations, these limitations initially proved quite difficult to overcome. When we adapted the literature aziridination[233] of styrene, $TsNH_2$ and hypochlorite by adding H_2O to solubilize the NaCl by-product, the reaction failed (Scheme 2.13).



Scheme 2.13. Trial reaction with $TsNH_2$ under homogeneous conditions.

Similarly, attempts to avoid the biphasic CH_2Cl_2/H_2O mixture used in the literature aziridination[234] of styrene with $NaNTsCl{\cdot}3H_2O$ (**254**) by switching CH_2Cl_2 to MeCN also did not work; the reaction remained heterogeneous with brown precipitates and no aziridine was detected (Scheme 2.14).



Scheme 2.14. Trial reaction with $NaNTsCl{\cdot}3H_2O$ under homogeneous conditions.

2.4 Use of 1,2-amino alcohols

Disappointed with these early findings, we sought an alternative strategy based on ring closure. We will return to direct alkene aziridinations in Chapter 3, where a successful solution to this problem was developed. We were attracted to Vicario *et al.*'s one step synthesis of 2-phenyl-1-tosylaziridine (**253**), from 2-amino-2-phenylethan-1-ol (**255**), as the reaction is not biphasic, and the reactants are all soluble in CH_2Cl_2 (Scheme 2.15).[235]

Scheme 2.15. Vicario *et al.*'s synthesis of 2-phenyl-1-tosylaziridine.

The synthesis of aziridines *via* ring closure of 1,2-amino alcohols also had a number of other benefits, such as the easy synthesis of 1,2-amino alcohols from α-amino acids.[236] Furthermore, if the 1,2-amino alcohol is chiral, ring closure readily gives a single enantiomer of the aziridine.[237]

While the batch reaction of 2-amino-2-phenylethan-1-ol (**255**) with TsCl worked in our hands, the rate of product formation was extremely slow and produced insoluble Et_3NHCl as a by-product. It was hoped that the rate of reaction could be improved by using increased amounts of DMAP, and that a change of solvent used would dissolve the Et_3NHCl formed. Pleasingly, when the amount of DMAP was increased to stoichiometric quantities (0.5 – 1 eq), and the solvent changed to $CHCl_3$, the trial reaction in batch was homogeneous and went to completion within one hour.

2.5 Optimization of the flow synthesis of 2-phenyl-1-tosylaziridine (253)

Since the trial batch reaction was successful, we carried out the same reaction under continuous flow. Two microreactors, a mixer module (LTF-MX) and a reaction module (LTF-V) were connected in series (Figure 2.2). The combined volume of the microreactors together with connecting tubes was 2.0 cm^3. The two inputs of the mixer module were connected to two computer controlled syringe pumps. Above atmosphere pressure was achieved with a back pressure regulator, and heating was achieved by immersing the connected microreactors in a silicone oil bath. To prevent further reaction after leaving the microreactor, the mixture was quenched into a stirred solution of saturated aq NH_4Cl.

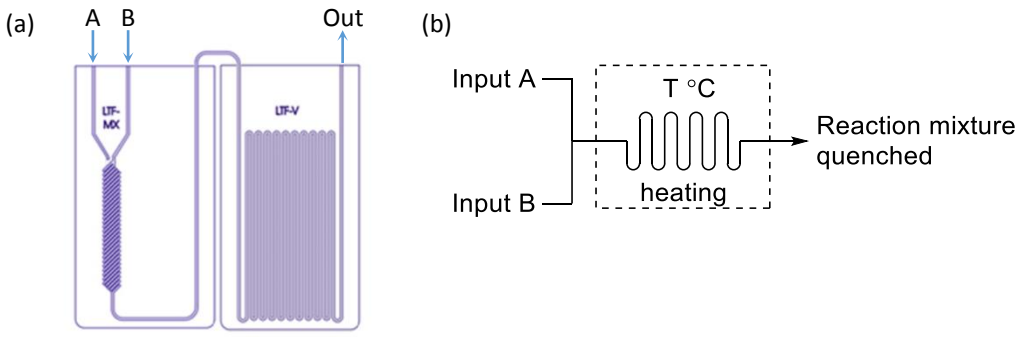
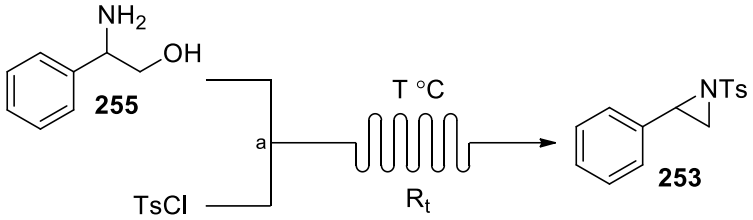


Figure 2.2. (a) Drawing; (b) schematic of the microreactor.

Table 2.1. Optimization of synthesis of 2-phenyl-1-tosylaziridine (**253**) in flow.



Entry	T (°C)	DMAP (eq)	Base (eq)	TsCl (eq)	R_t (min)	Yield[b] (%)
1	21	0.5	Et_3N (4.5)	2.0	8	30
2	21	0.5	Et_3N (4.5)	2.5	8	51
3	21	0.5	Et_3N (4.5)	2.5	13	53
4	21	0.5	Et_3N (4.5)	2.5	40	67
5	30	0.5	Et_3N (3.8)	2.5	40	53
6	**30**	**0.5**	**Et_3N (4.5)**	**2.5**	**40**	**73**
7	30	0.5	Et_3N (5.3)	2.5	40	74
8	30	0.5	DBU (4.5)	2.5	40	trace
9	30	0	Et_3N (4.5)	2.5	40	trace
10	30	0.3	Et_3N (4.5)	2.5	40	70
11	30	1.0	Et_3N (4.5)	2.5	40	70
12	30	1.0	Et_3N (4.5)	3.0	40	77
13	35	0.5	Et_3N (4.5)	2.5	40	70
14	30	0.3	Et_3N (4.5)	2.3	40	61
15	50	0.5	Et_3N (4.5)	2.5	8	60
16	80	0.5	Et_3N (4.5)	2.5	8	47
17	80	0.5	Et_3N (4.5)	2.5	4	52

[a] 2-amino-2-phenylethan-1-ol (1 eq), DMAP (eq) and base (eq) were dissolved in $CHCl_3$; TsCl (eq) was dissolved in $CHCl_3$. [b] Isolated yield after chromatography.

The results of the optimization are shown in Table 2.1. As entries 1 and 2 show, increasing the number of equivalents of TsCl from 2.0 eq to 2.5 eq increased the yield. Attempts to further increase the equivalents of TsCl under more optimized conditions (entry 12 compared with entry 6) did not improve the yield by much. Furthermore, the increase in concentration of TsCl posed technical problems for the syringe pumps, causing TsCl precipitation around the syringe pump seals which would damage the syringe pumps.

As entries 2, 3 and 4 show, increasing the residence time R_t increased the isolated yield. The residence time is the average amount of time a single molecule spends in the microreactor before quenching. It was not readily possible to alter the residence time beyond 40 min, due to the limitations of the pumps used.

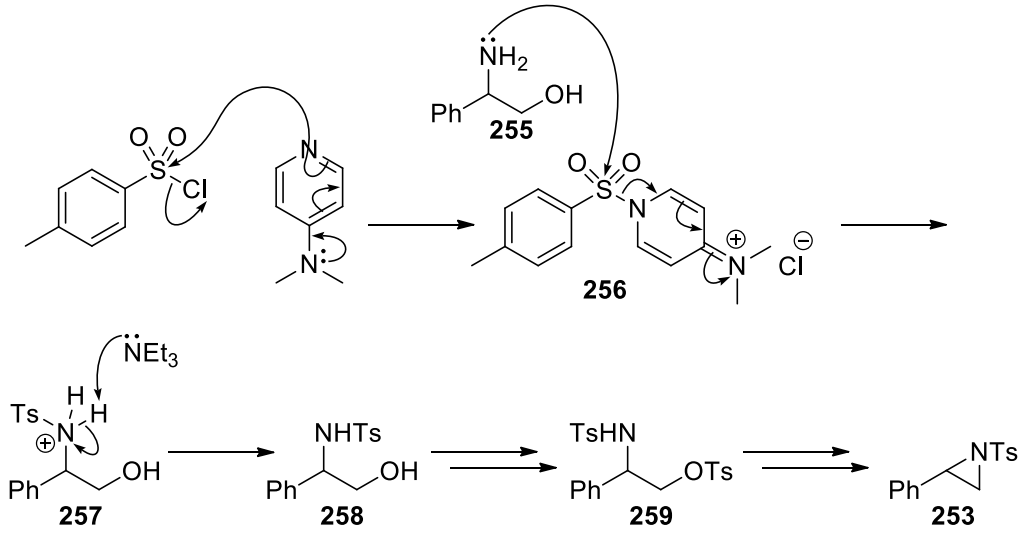
Increasing the temperature from 21 °C (entry 4) to 30 °C (entry 6) increased the yield, but further temperature rises (entry 13) did not further improve the yield. In fact, when the temperature was further increased, the reaction did occur faster, but the aziridine began to decompose, necessitating a concurrent reduction in the residence time (entries 15, 16 and 17).

The reaction did not work in the absence of DMAP (entry 9), and decreasing the amount of DMAP and TsCl together lead to lower yields (entry 14). It was found necessary to keep the quantities of TsCl and DMAP in careful balance. Ideally, (2+x) equivalents of TsCl required x equivalents of DMAP to be present in order to avoid any remaining TsCl after quenching. When only the amount of equivalents of DMAP was reduced (entry 10), the yield was affected slightly, but purification became much more difficult due to remaining TsCl even after quenching.

Decreasing the number of equivalents of NEt_3 lowered the yield (entry 5), but increasing the number of equivalents of NEt_3 beyond 4.5 eq (entry 7) did not improve the yield significantly. Changing the base from NEt_3 to DBU caused the reaction not to work (entry 8). Preliminary studies using other bases such as pyridine, 2,4,6-collidine, 2,6-lutidine and piperidine were also unproductive (details not shown).

Thus, the optimal conditions for the synthesis of aziridine **253** from 1,2-amino alcohol **255** was found to be at 30 °C, with 0.5 eq of DMAP, 4.5 eq of NEt_3, 2.5 eq of TsCl, with a residence time of 40 min (entry 6).

A possible mechanism for the synthesis of aziridine **253** is shown in Scheme 2.16. DMAP first reacts with TsCl to form an active tosylating intermediate **256**, which then further reacts with the 1,2-amino alcohol. Some evidence in support of this mechanism is that the $[DMAPTs]^+Cl^-$ complex **256** can be isolated, and this complex has been shown to tosylate amines and alcohols efficiently.[238]



Scheme 2.16. Proposed mechanism in the synthesis of aziridine **253**.

2.6 Continuous flow synthesis of other aziridines from 1,2-amino alcohols

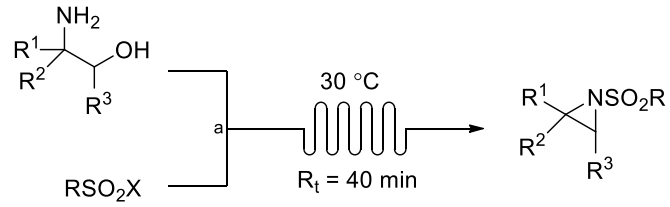
Next, we attempted the continuous flow synthesis of other aziridines from 1,2-amino alcohols using the optimized conditions detailed in section 2.5. Gratifyingly, it was possible to vary both the sulfonyl protecting group on the aziridine nitrogen, as well as the type of 1,2-amino alcohol used (Table 2.2).

The best yields were achieved with 1,2-amino alcohols that had an amine flanked by a non-bulky aromatic group (R^1 = Ar; R^2 = R^3 = H; entries 1, 2, 5 – 8). 1,2-amino alcohols with R^1 = alkyl, R^2 = R^3 = H, gave moderate yields (entries 13 and 14). Attempts to synthesize aziridines **274** and **279** were unsuccessful, with only trace product observed (entries 10 and 15).

When the synthesis of 1-mesyl-2-phenylaziridine (**269**) was attempted using MsCl, a moderate yield of 54% was obtained (entry 3). Switching from MsCl to Ms_2O did not improve the yield (entry 4), but when the base was changed from NEt_3 to DBU, a significantly higher yield of 74% was obtained (entry 5). This combination of Ms_2O and DBU gave much higher yields compared to MsCl / NEt_3 in the synthesis of a range of mesyl protected aziridines (see also section 2.10). However, it was necessary to use a mixed solvent system (CH_2Cl_2:$CHCl_3$, 1:1) to keep Ms_2O in solution. Unfortunately, Ts_2O and $^pNs_2O$ were too insoluble in all solvent systems tried to explore $(ArSO_2)_2O$ / DBU more generally.

When chiral (*S*)-phenylglycinol (*S*)-(**255**) was used to make chiral (*S*)-**253**, no detectable racemization could be observed; only the *S*-enantiomer was formed as indicated by chiral HPLC. The absolute configuration was confirmed by comparing the sign and magnitude of the optical rotation to literature values.[239]

Table 2.2. Synthesis of various aziridines from 1,2-amino alcohols.



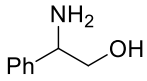
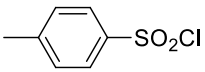
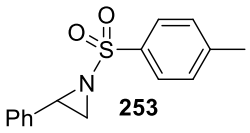
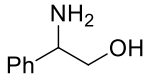
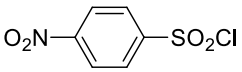
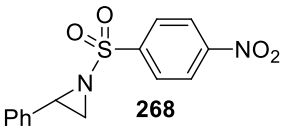
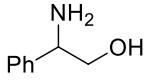
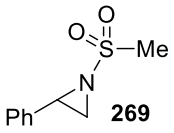
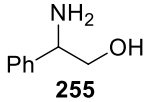
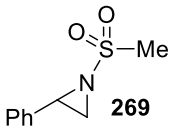
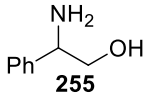
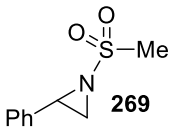
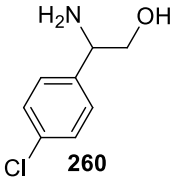
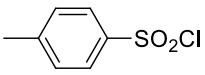
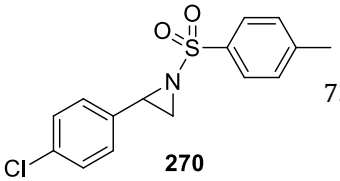
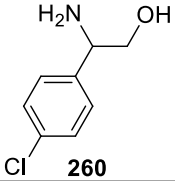
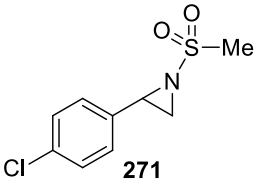
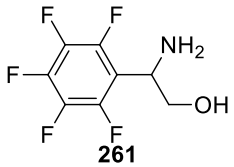
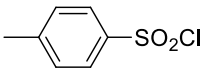
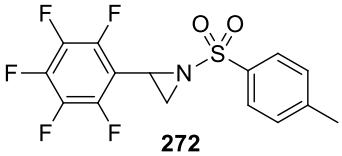
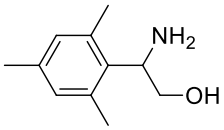
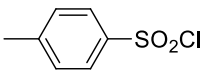
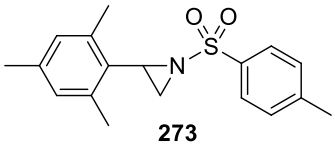
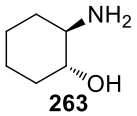
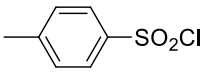
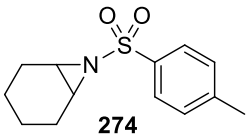
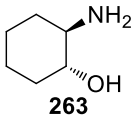
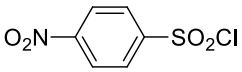
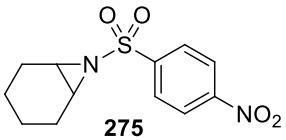
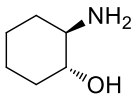
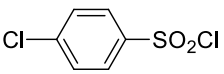
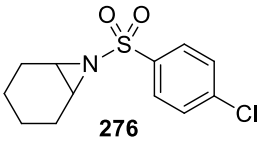
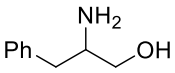
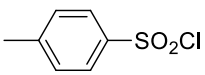
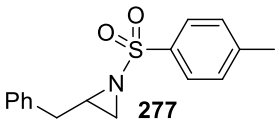
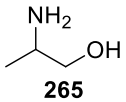
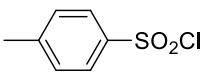
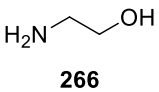
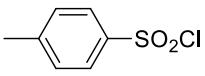
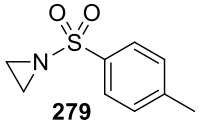
Entry	1,2-amino alcohol	RSO_2X	Aziridine	Yield[b] (%)
1	 **255**		 **253**	73
2	 **255**		 **268**	59
3	 **255**	$MeSO_2Cl$	 **269**	54
4	 **255**	$MeSO_2—OMs$	 **269**	50
5	 **255**	$MeSO_2—OMs$	 **269**	74[c]
6	 **260**		 **270**	73
7	 **260**	$MeSO_2—OMs$	 **271**	71[c]

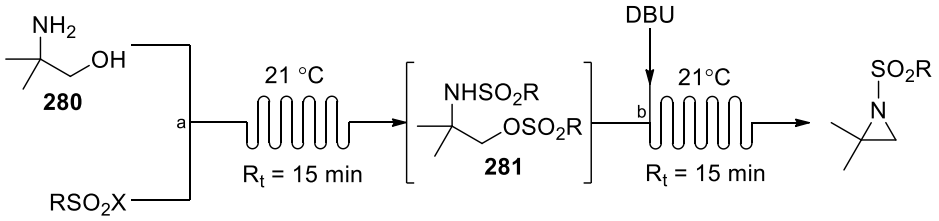
Table 2.2. Synthesis of various aziridines from 1,2-amino alcohols (continued).

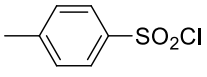
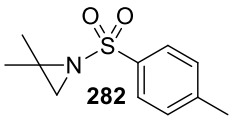
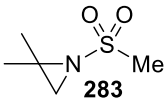
Entry	1,2-amino alcohol	RSO_2X	Aziridine	Yield[b] (%)
8	 **261**		 **272**	77
9	 **262**		 **273**	39
10	 **263**		 **274**	trace
11	 **263**		 **275**	68
12	 **263**	 **267**	 **276**	30
13	 **264**		 **277**	42
14	 **265**		 **278**	51
15	 **266**		 **279**	trace

[a] 1,2-amino alcohol (1 eq), DMAP (0.5 eq) and NEt_3 (4.5 eq) were dissolved in $CHCl_3$; RSO_2Cl (2.5 eq) was dissolved in $CHCl_3$; Ms_2O was dissolved in CH_2Cl_2 / $CHCl_3$ 1:1. [b] Isolated yield after chromatography. [c] DBU (4.5 eq) was used as base.

An attempt to synthesize *gem*-dimethyl aziridines where $R^1 = R^2 = Me$ was made using this continuous flow methodology, but this was not particularly successful. However, it was found that the product could be obtained if the sulfonylation of the 1,2-amino alcohol and the subsequent ring closure were separated into 2 operations using a three input, two stage reactor (Table 2.3). This was achieved using 2.1 equivalents of DMAP with 2.1 equivalents of TsCl to first disulfonylate 2-amino-2-methyl propan-1-ol (**280**) in the first section of the reactor. Ring closure of **281** was then effected with DBU in the second section of the reactor. In the absence of DBU, very little ring closure product was observed by mass spectrometry. Whilst the Thorpe-Ingold effect[240] might have been expected to improve yields in synthesis of *gem*-dimethyl aziridines due to angle compression and the reduction in the number of degrees of freedom, this was not the case. This perhaps suggests that *N*-tosylation is the rate determing step, not ring closure.

Table 2.3. Synthesis of 2,2-dimethylaziridines with a three input, two stage microreactor.



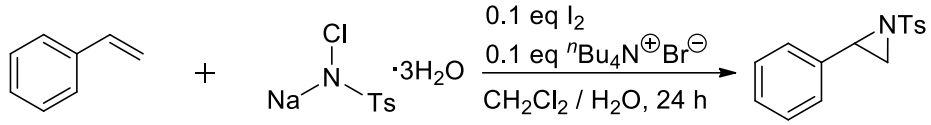
Entry	RSO_2X	Aziridine	Yield[c] (%)
1		 **282**	36
2	$MeSO_2—OMs$	 **283**	34

[a] 2-amino-2-methylpropan-1-ol (1 eq) and DMAP (2.1 eq) were dissolved in $CHCl_3$; TsCl (2.1 eq) was dissolved in $CHCl_3$; Ms_2O (2.1 eq) was dissolved in CH_2Cl_2 / $CHCl_3$ 1:1. [b] DBU (4.5 eq) in $CHCl_3$. [c] Isolated yield after chromatography.

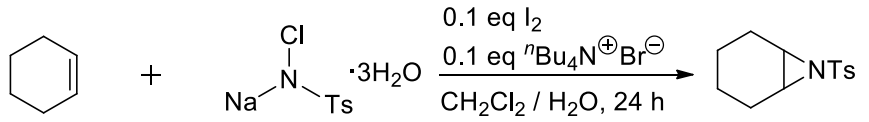
2.7 Ring opening reactions of aziridines

Next, we explored the ring opening reactions of these aziridines with a range of potential nucleophiles. Our ultimate aim was to telescope the aziridine formation with such ring opening processes (section 2.10).

First, we synthesized multi-gram quantities of both the non-symmetrical 2-phenyl-1-tosylaziridine (**253**) and the symmetrical 7-tosyl-7-azabicyclo[4.1.0] heptane (**274**). For convenience, we chose to synthesize these aziridines under batch conditions[33, 234] (Schemes 2.17 and 2.18), in part because styrene and cyclohexene were much cheaper than the corresponding 1,2-amino alcohols. It should be noted that these reactions produced precipitates, were biphasic, and hence were unsuitable for carrying out under continuous flow methodology.

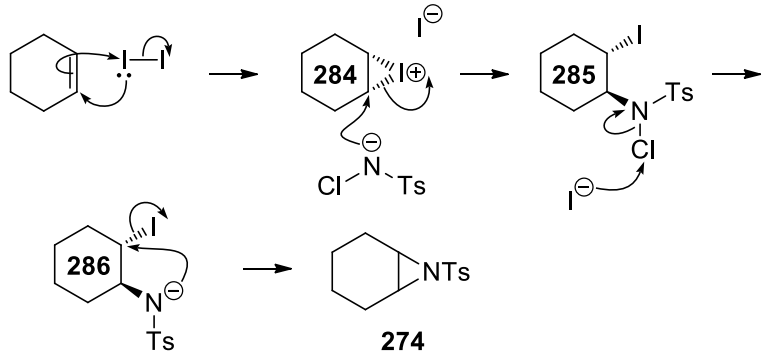


Scheme 2.17. Synthesis of 2-phenyl-1-tosylaziridine (**253**) in batch.



Scheme 2.18. Synthesis of 7-tosyl-7-azabicyclo[4.1.0]heptane (**274**) in batch.

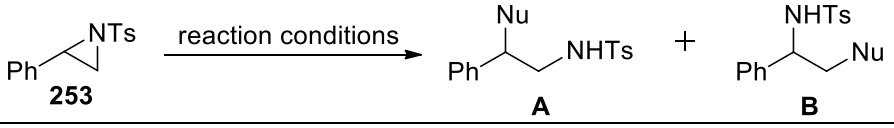
This iodine-catalysed aziridination of alkenes proceeds by a different mechanism (Scheme 2.19). Iodine first forms an iodonium cation **284** with the alkene, which then is attacked by NaNTsCl, before further cyclization.



Scheme 2.19. Mechanism for the aziridination of cyclohexene with NaNTsCl.

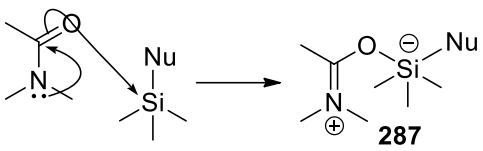
With large quantities of aziridine **253** in hand, we screened ring opening with a variety of nucleophiles under batch conditions[163, 183, 187-188] (Table 2.4). A key aim was to identify conditions to achieve good regiocontrol. Surprisingly, when we repeated work by Wu *et al.*[183], we obtained low conversion, as well as a mixture of regioisomers resulting from predominant attack at the less hindered carbon (entry 1). Wu *et al.* had reported high yields with predominant attack at the more hindered benzylic position. Regioisomers **A** and **B** were assigned using COSY and HMBC experiments.

Table 2.4. Screening of ring opening of **253** with various nucleophiles.



Entry	Nu	Conditions	Conversion (%)[a]
1	Cl	12 eq Me_3SiCl; DMF; 40 °C; 24 h.	37 (**A**/**B** = 1/9).
2	Cl	1.1 eq $^tBuMe_2SiCl$; DMF; 40 °C; 24 h.	70 (only **A** observed).
3	Cl	HCl (2M in Et_2O); 40 °C; 1h.	94 (only **A** observed).
4	N_3	12 eq Me_3SiN_3; DMF; 40 °C; 24 h.	35 (**A**/**B** = 7/3).
5	OH	3 eq H_2SO_4; 22 eq H_2O; acetone; 40 °C; 1 h.	92 (only **A** observed).
6	OMe	3 eq H_2SO_4; MeOH; 40 °C; 1 h.	97 (only **A** observed).
7	OMe	3 eq AcOH; MeOH; 40 °C; 1h.	0

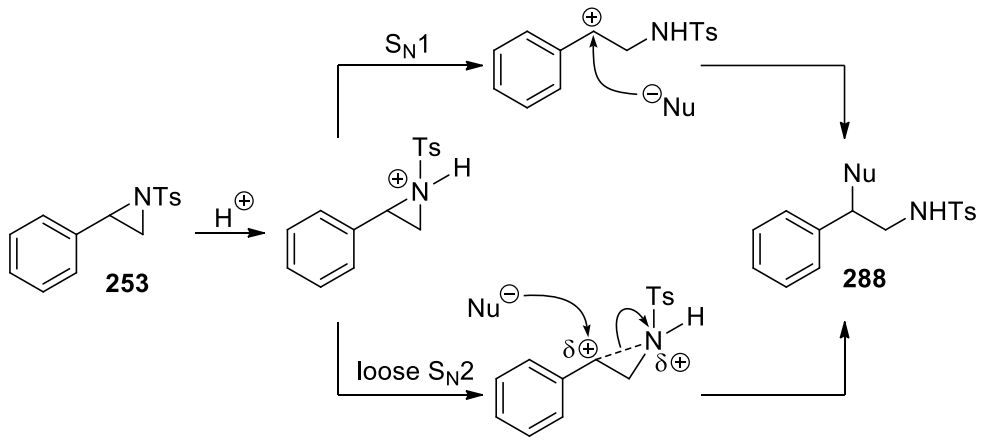
[a] Conversion into **A** + **B** determined by ^1H NMR spectroscopy.



Scheme 2.20. Formation of DMF/Me_3SiNu complex.

As the actual nucleophile in ring openings of aziridines with Me_3SiNu is thought to be a DMF/Me_3SiNu complex[183, 241] **287** (Scheme 2.20), we wondered if changing the chloride source from Me_3SiCl to the bulkier $^tBuMe_2SiCl$ would alter the regioselectivity of the ring opening. Interestingly, we obtained attack only at the benzylic position under these conditions (entry 2). With Me_3SiN_3, we obtained the same mixture of regioisomers (**A**/**B** = 7/3) as reported by Wu, but the reaction did not go to completion even after 24 h with an excess of reagent (entry 4). This perhaps suggests that with Me_3SiNu (Nu = Cl or N_3), there is a competition between two reaction pathways which can favour either the **A** or **B** regioisomer with incomplete regioselectivity. With $^tBuMe_2SiCl$, the nitrogen on the aziridine might first complex with the silicon to give a positive charge, which favours nucleophilic attack at the benzylic position with complete regioselectivity.

Complete regioselectivity for attack at the benzylic position was achieved under strong acid catalysis, with the additional benefit that reactions were all much quicker (entries 3, 5 and 6). Using a weaker acid such as AcOH lead to no product formation (entry 7). The regioselectivity of the H^+ catalysed ring openings can be rationalized either by a S_N1 process, or by a loose S_N2 process (Scheme 2.21). No attempts to open aziridines with N_3^- in the presence of acid were made, as HN_3 is both extremely toxic as well as potentially explosive. However, convenient conditions for the complete regioselective ring opening at the benzylic position of **253** by chloride, water and methanol were identified through this study.



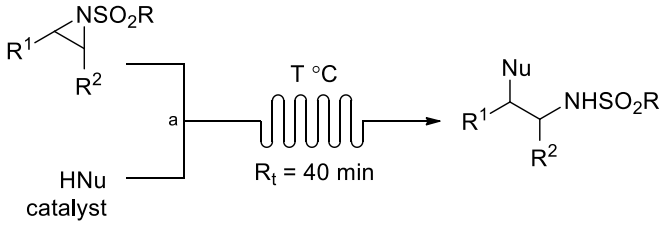
Scheme 2.21. Rationalization for complete regioselectivity.

2.8 Ring opening reactions of aziridines under continuous flow

Next, we attempted to apply continuous flow methodology to the ring opening of aziridines (Table 2.5). In order to get complete conversion with a residence time of 40 min, we had to increase the temperature to 70 °C for *N*-tosyl aziridines **253** and **274** (entries 1 – 7). Interestingly, *N*-mesyl aziridine **269** was much more reactive, undergoing complete conversion within 40 min at 21 °C (entries 9 – 12).

Oxygen and carbon nucleophile ring openings could be effected under Brønsted acid catalysis with strong acids having non-nucleophilic counterions such as H_2SO_4 and MsOH (entries 2, 3, 4, 6, 7, 9, 10 for oxygen nucleophiles; entries 11, 12 for carbon nucleophiles). Chloride ring openings were effected using HCl in diethyl ether / chloroform as both acid catalyst and nucleophile source (entries 1, 5). Fluoride ring opening of *N*-*p*nosyl aziridine **275** could also be achieved within 40 min at 21 °C (entry 8), using an adaptation of the $BF_3{\cdot}OEt_2$ / ^{i}PrOH protocol developed by Ding *et al.*.[242] The yield of 63% for this example (entry 8) is closely comparable to Ding *et al.*'s yield of 68% for the fluoride ring opening of the *N*-Bs derivative under batch conditions.

Table 2.5. Ring-opening of aziridines in flow.



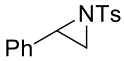
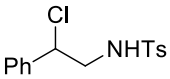
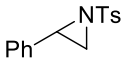
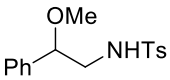
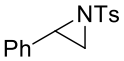
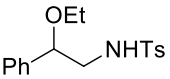
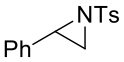
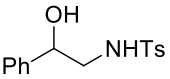
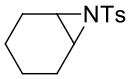
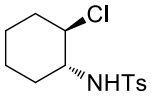
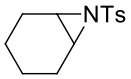
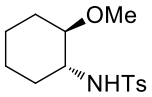
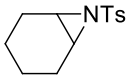
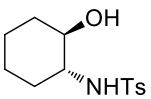
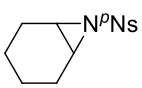
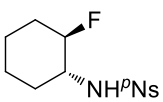
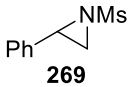
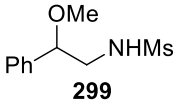
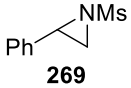
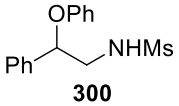
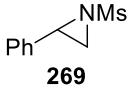
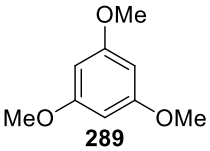
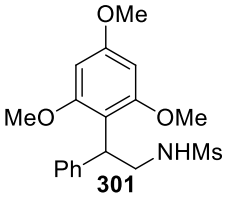
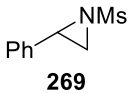
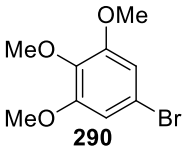
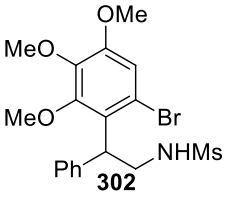
Entry	Aziridine	HNu	Catalyst	T (°C)	Product	Yield[b] (%)
1	 **253**	HCl	–	70	 **291**	69
2	 **253**	HOMe	H_2SO_4	70	 **292**	97
3	 **253**	HOEt	MsOH	70	 **293**	39
4	 **253**	HOH	H_2SO_4	70	 **294**	98
5	 **274**	HCl	–	70	 **295**	98
6	 **274**	HOMe	H_2SO_4	70	 **296**	72
7	 **274**	HOH	H_2SO_4	70	 **297**	75
8	 **275**	"HF"	$Et_2O{\cdot}BF_3$ $^{i}PrOH$	21	 **298**	63

Table 2.5. Ring-opening of aziridines in flow (continued).

Entry	Aziridine	HNu	Catalyst	T (°C)	Product	Yield[b] (%)
9	 **269**	HOMe	H_2SO_4	21	 **299**	73
10	 **269**	HOPh	MsOH	21	 **300**	53
11	 **269**	 **289**	MsOH	21	 **301**	51
12	 **269**	 **290**	MsOH	21	 **302**	14

[a] For ring openings with HCl: aziridine was dissolved in $CHCl_3$; HCl in Et_2O / $CHCl_3$. For ring openings with MeOH or EtOH: aziridine in $CHCl_3$; H_2SO_4 in MeOH or EtOH. For ring openings with H_2O: aziridine in acetone; H_2O and H_2SO_4 in acetone. For ring openings with "HF": aziridine in $CHCl_3$; ^{i}PrOH and $BF_3{\cdot}OEt_2$ in $CHCl_3$. For ring openings with ArOH or ArH: aziridine was dissolved in $CHCl_3$; ArOH or ArH and MsOH in $CHCl_3$. [b] Isolated yield after chromatography.

Unfortunately, Ding *et al.*'s protocol did not work in the fluoride ring opening of aromatic aziridines such as **253** or **269**, which is not surprising considering they only reported it working for aziridines with alkyl (or benzyl) groups at the 2-position of the aziridine.[242]

With unsymmetrical 2-phenyl aziridines **253** and **269**, only the regioisomer formed from attack at the benzylic position was observed. This was confirmed in all cases by 2D NMR experiments including ^{1}H COSY and ^{1}H – ^{13}C HMBC.

All ring-opened products formed from 2-phenyl aziridines showed a three bond coupling between the N*H* and the CH_2N in the ^{1}H COSY spectrum. In the case of ring openings with alcohols such as MeOH, a three bond coupling between the OCH_2R and Ph*C*H could be detected in the ^{1}H–^{13}C HMBC spectrum. An example is given in Figure 2.3, where the spectra of **299** in $CDCl_3$ is given; the MeO and $MeSO_2$ methyl groups were distinguished by chemical shift and ^{1}H–^{13}C HMBC experiments.

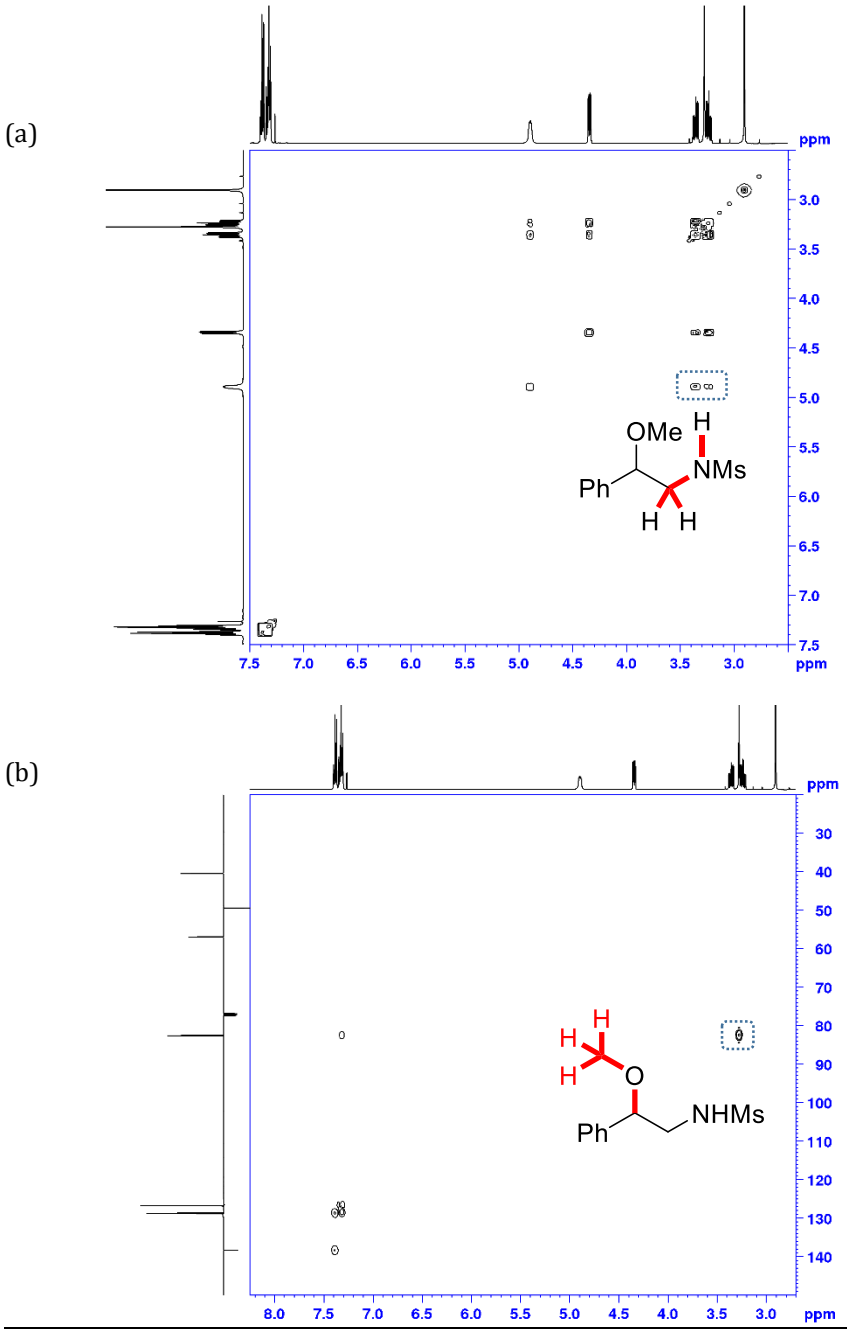


Figure 2.3. Illustrative 2D NMR spectra of **299** in $CDCl_3$. (a) ^{1}H COSY. (b) ^{1}H–^{13}C HMBC.

For the Brønsted acid catalysed Friedel-Crafts alkylation with 1,3,5-trimethoxy benzene (**289**), the regiochemical outcome in **301** was confirmed by X-ray crystallography (Figure 2.4). While the Friedel-Crafts alkylation of aziridines with arenes is known, most of these processes involve the use of Lewis acids.[207]

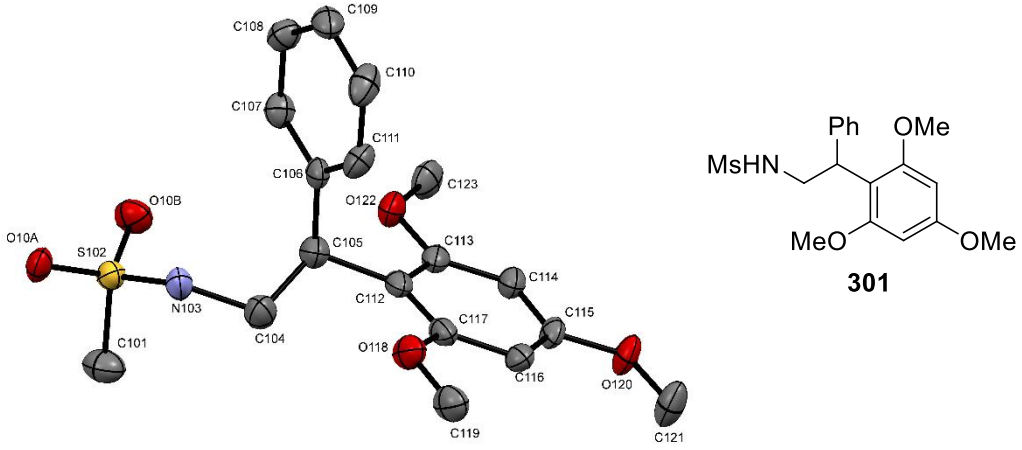


Figure 2.4. X-ray crystal structure of **301** showing regiochemical outcome.

Only the *trans* stereoisomer was observed in ring opening of the symmetrical aziridines **274** and **275**. Mechanistically, a *trans* stereochemical outcome would be expected due to S_N2 attack of the nucleophile from opposite the aziridine ring.[243] The *trans*-stereochemistry of ring opened products **295**, **296**, **297**, and **298** were confirmed by the large $^3J_{HH}$ coupling constants between the diaxial hydrogens attached to the carbons bearing the diequatorial substituents.

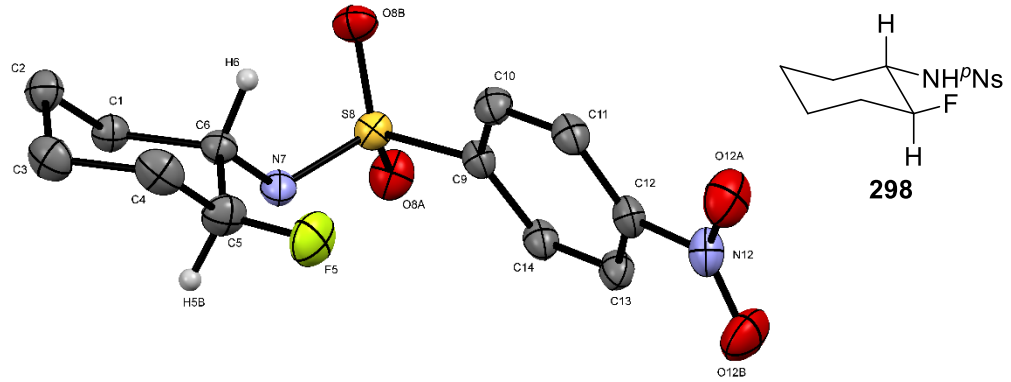
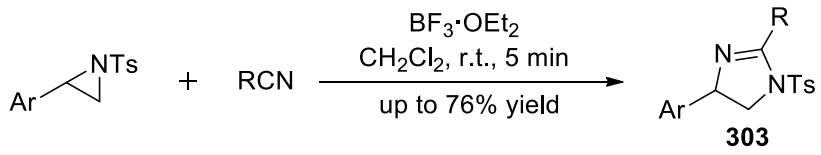


Figure 2.5. X-ray crystal structure of **298** showing *trans*-stereochemistry.

The NMRs of these compounds matched data given in literature where the stereochemistry was assigned as *trans*.[183, 244] In the case of **298**, this was further confirmed by X-ray crystallography (Figure 2.5).

2.9 Formal [3+2] cycloaddition of 2-arylaziridines with nitriles in flow

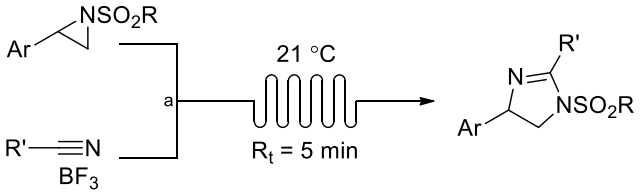
The Lewis acid catalysed formal [3+2] cycloaddition of *N*-tosyl 2-arylaziridines with nitriles was previously reported by Singh *et al.* (Scheme 2.22).[245] As their reaction conditions were extremely mild and rapid, with reaction at room temperature in less than 5 min, we wondered if we could adapt their protocol to flow. This offers an attractive route to these imidazolines.

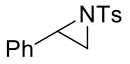
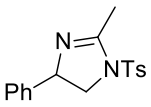
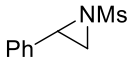
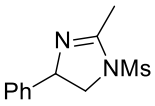
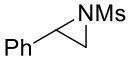
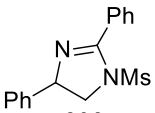
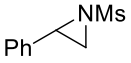
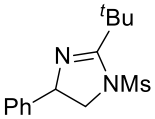
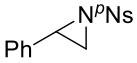
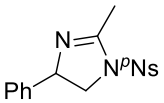
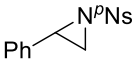
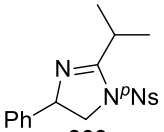
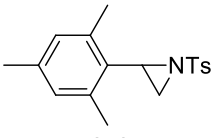
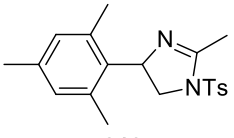


Scheme 2.22. Singh *et al.*'s formal [3+2] cycloaddition of *N*-tosyl aziridines with nitriles.

When we effected the formal [3+2] cycloaddition of a range of *N*-sulfonyl 2-arylaziridines with a variety of nitriles at room temperature using a 5 min residence time, we obtained imidazolines in moderate to good yields (Table 2.6). A single regioisomer was seen in all cases. However, it was not possible to assign the regiochemistry of the imidazolines by 2D NMR experiments such as ^{1}H COSY and ^{1}H–^{13}C HMBC; three bond couplings in imidazolines obtained from attack at either carbon of the aziridine would be expected to be very similar.

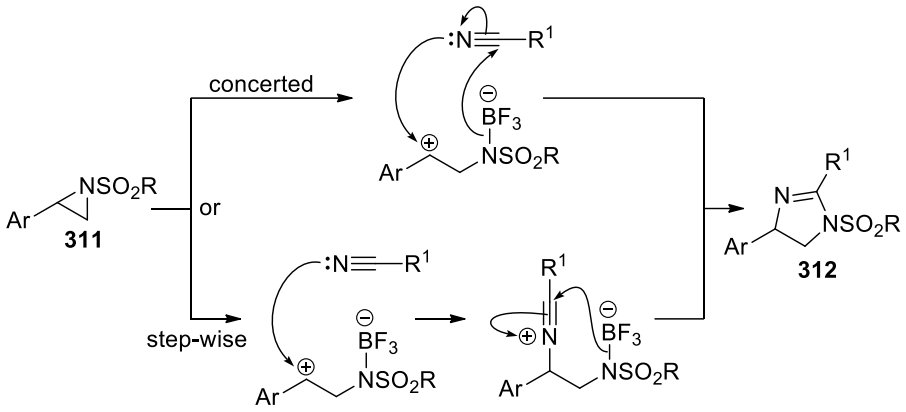
Table 2.6. Formal [3+2] cycloaddition of aziridines with nitriles in flow.



Entry	Aziridine	R'CN	Product	Yield[b] (%)
1	 **253**	MeCN	 **304**	73
2	 **269**	MeCN	 **305**	71
3	 **269**	PhCN	 **306**	58
4	 **269**	^{t}BuCN	 **307**	48
5	 **268**	MeCN	 **308**	68
6	 **268**		 **309**	81
7	 **273**	MeCN	 **310**	53

[a] Aziridine (1 eq) was dissolved in CH_2Cl_2; $Et_2O{\cdot}BF_3$ (5.0 eq) and R'CN (5.0 eq) was dissolved in CH_2Cl_2. [b] Isolated yield after chromatography.

Attempted NOESY experiments were also inconclusive. However, the mechanism through which the formal [3+2] cycloaddition occurs likely involves attack of the nitrile nitrogen at the benzylic carbon (Scheme 2.23).



Scheme 2.23. Proposed mechanism for the formal [3+2] cycloaddition.

This mechanism is supported by studies done by Singh *et al.*[245], in which the chirality of (*R*)-2-phenyl-1-tosylaziridine (**253**) was lost leading to a racemic imidazoline. Furthermore, we obtained X-ray crystal structures of **305** (Figure 2.6) and **306** (Figure 2.7), which confirm the regiochemical outcome in these cases. Since the ^{1}H NMR spectra of all imidazolines were similar, with a characteristic peak for ArC*H* at around 5 ppm and two peaks for CH*H* and C*H*H at 3 – 4 ppm, we were confident that nitrile attack occurred at the benzylic carbon in all cases.

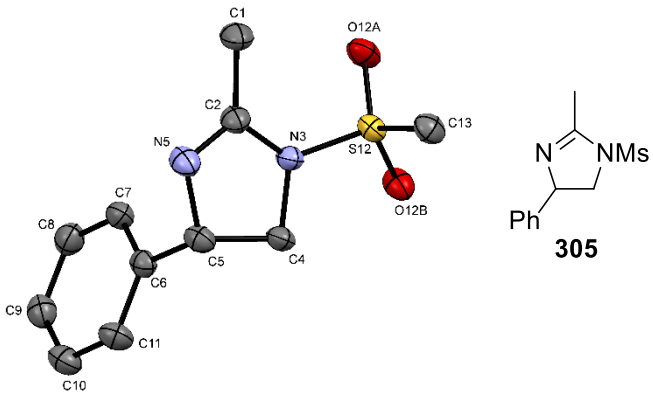


Figure 2.6. X-ray crystal structure of **305**.

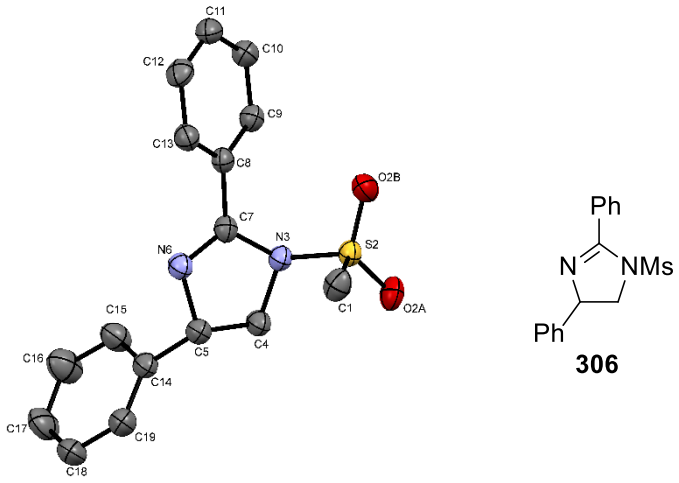


Figure 2.7. X-ray crystal structure of **306**.

2.10 Continuous flow cascade reactions involving aziridine intermediates

With the synthesis of various aziridines achieved in flow (section 2.6), and ring opening and cycloaddition chemistries under continuous flow methodology developed (sections 2.8 and 2.9), we set about combining these methods using a two stage, three-input glass microreactor (Figure 2.8).

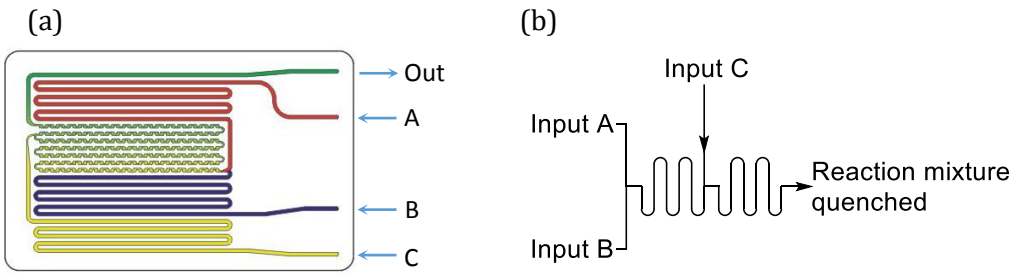
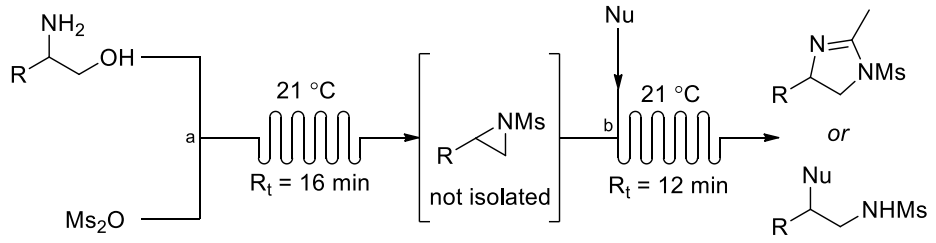


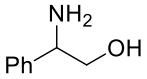
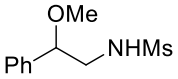
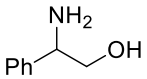
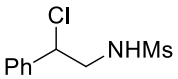
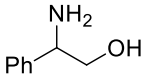
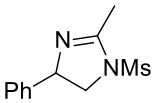
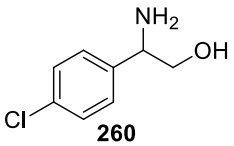
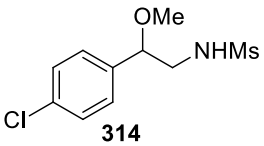
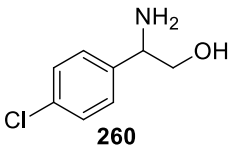
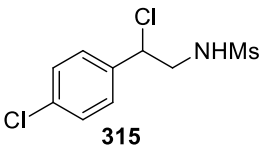
Figure 2.8. Two stage, three input microreactor. (a) drawing (b) schematic

This proved more problematic than we initially envisaged. Attempts to use RSO_2X = TsCl, ^{p}NsCl or MsCl as the sulfonylating agent produced large amounts of chloride anion which competed in the subsequent ring opening step. This resulted in a large amount of chloride ring opened product regardless of nucleophile used in the subsequent cascade step.

To overcome these problems, we switched to a different activator that would produce a much weaker nucleophile as by product. Ms_2O was the only reagent which produced acceptable yields in these cascade processes (Table 2.7).

Table 2.7. Cascade reactions involving aziridine intermediates.



Entry	1,2-amino alcohol	Nu	Catalyst	Product	Yield[c] (%)
1	 **255**	MeOH	MsOH	 **299**	61
2	 **255**	HCl	–	 **313**	58
3	 **255**	BF_3	MeCN	 **305**	42
4	 **260**	MeOH	MsOH	 **314**	57
5	 **260**	HCl	–	 **315**	53

[a] 1,2-amino alcohol (1 eq), DMAP (0.5 eq) and DBU (4.5 eq) were dissolved in $CHCl_3$; Ms_2O was dissolved in $CH_2Cl_2/CHCl_3$ 1:1. [b] Nucleophile (and catalyst if necessary) were dissolved in the appropriate solvent. [c] Isolated yield after chromatography.

Other sulfonyl anhydrides were tried, such as $^{p}Ns_2O$, $^{o}Ns_2O$ and Ts_2O, but these sulfonyl anhydrides were too insoluble in all solvent systems tested to be suitable for flow chemistry. A further limitation with this chemistry was the requirement to use large amounts of acid catalyst (8 eq), since there was 4.5 equivalents of base from the ring closure step which had to be neutralized before Brønsted acid activation could occur.

Despite these problems, we managed to explore a number of examples of nucleophilic ring opening of aziridine intermediates generated from 1,2-amino alcohols **255** and **260** under continuous flow methodology (Table 2.7). The best yield was achieved when the nucleophile was used as a solvent (entries 1 and 4). Moderate yields were achieved with HCl (entries 2 and 5).

Other 1,2-amino alcohols were tried using this telescoped flow methodology, but it was not possible to isolate and purify the ring opened products from the reaction mixture by column chromatography. These limitations in the cascade ring opening of aziridines generated from 1,2-amino alcohols led to the direction of studies detailed in Chapter 3.

2.11 Conclusions

We have achieved a rapid and general route to aziridines through ring closure of the corresponding 1,2-amino alcohols using continuous flow methodology. Using this method, a range of substitution patterns are accessible, with 13 examples of aziridines synthesized in flow with moderate to good yields.

We also explored various reactions of aziridines under continuous flow methodology. Ring opening of aziridines with various oxygen, carbon and halide nucleophiles was successful in flow, with 12 examples of ring opened products. Formal [3+2] cycloadditions with a variety of nitriles in flow was also possible, with 7 examples of imidazolines synthesized. Under the developed conditions, complete regiocontrol in the reactions of 2-arylaziridines was seen, and complete stereocontrol witnessed in ring openings of 7-azabicyclo[4.1.0]heptane aziridine derivatives.

The synthesis of aziridines from 1,2-amino alcohols and its subsequent ring opening can be telescoped in flow, limiting exposure to this potentially hazardous class of electrophilic reagents. Using this new flow methodology, the rapid synthesis of 5 ring opened products directly from the 1,2-amino alcohol was achieved, without having to isolate and purify the intermediate aziridine.

The work discussed in this chapter was published in Organic Letters in 2015.[246]

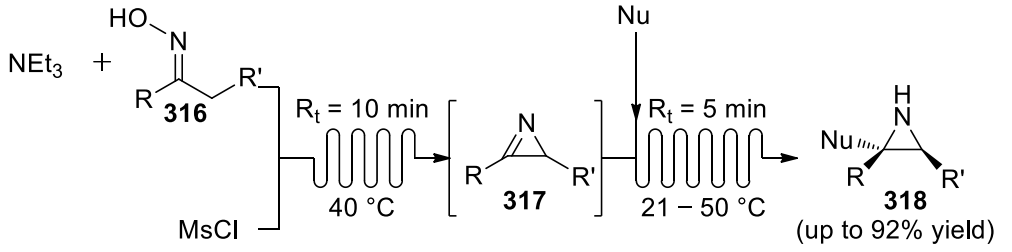
Chapter 3:

Aziridination of Alkenes and Subsequent Cascade Reactions in Flow

3.1 Introduction

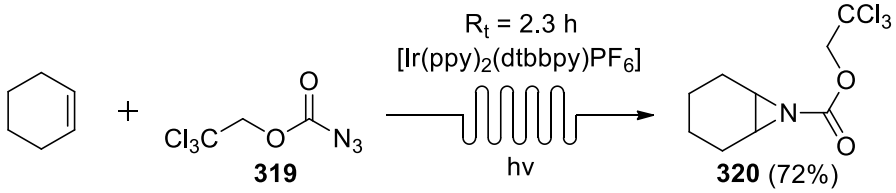
After our paper on the generation and ring opening of aziridines in telescoped continuous flow processes was published in July 2015, a number of other papers emerged on the continuous flow synthesis of aziridines. Booker-Milburn *et al.* conducted further investigation into the flow synthesis of tricyclic aziridines by the rearrangement of *N*-functionalized pyrroles (Scheme 2.7).[247]

Baumann *et al.* effected the synthesis of 2*H*-azirine **317** from the Neber rearrangement of oxime **316** in flow, and subsequently reacted the 2*H*-azirine in a telescoped process with nucleophiles to give aziridine **318** (Scheme 3.1).[248]



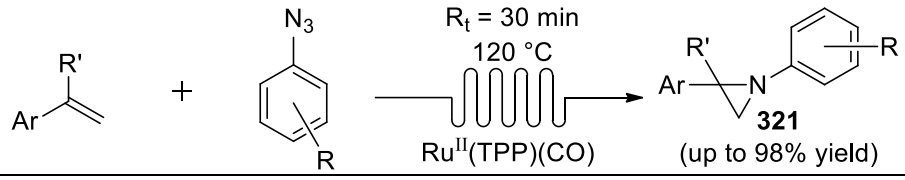
Scheme 3.1. Baumann *et al.*'s in flow synthesis of aziridines.

Yoon *et al.* aziridinated cyclohexene with 2,2,2-trichloroethyl azidoformate (**319**) to give the aziridine using photochemical catalysis in a flow reactor (Scheme 3.2). Interestingly, they found that the reduced dimensionality of a flow reactor increased the photon flux and increased efficiencies, leading to a shorter reaction time; the residence time was shortened from 4 h in batch to 2.3 h in flow.[249]



Scheme 3.2. Yoon *et al.*'s in flow aziridination of cyclohexene.

Similarly, Puglisi *et al.* aziridinated aromatic alkenes with a range of arylazides to give *N*-aryl aziridine **321** (Scheme 3.3).[250] However, their procedure required the use of the alkene as solvent, as well as high temperatures.



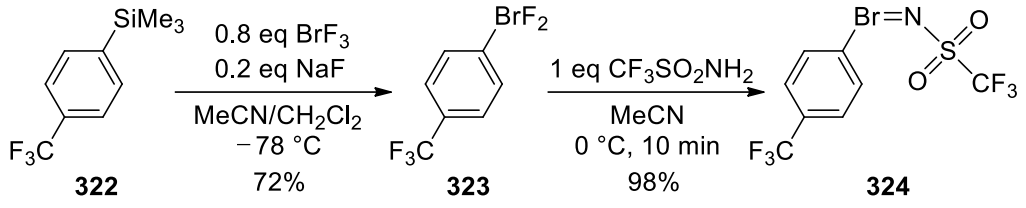
Scheme 3.3. Puglisi *et al.*'s in flow synthesis of aziridines using arylazides.

The approaches above did not seem suitable for us to try and improve cascade type processes in which the aziridine is generated and further reacted *in situ*. Moreover, we did not have access to flow equipment which could withstand high temperatures or allow photoirradiation.

We remained interested in the direct aziridination of alkenes using continuous flow methodology, with a view to coupling it with ring opening reactions to provide telescoped, cascade processes to give functionalized products directly from the alkenes. One of the key challenges is that we must use soluble aziridinating agents, some of which are described in the following section.

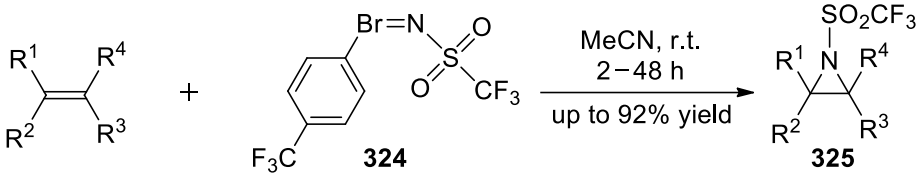
3.2 Soluble aryliminobromane and aryliminoiodanes

In 2007, Ochiai *et al.* prepared a soluble aryliminobromane that attracted our interest. Starting from trimethyl(4-(trifluoromethyl)phenyl)silane (**322**), reaction with bromine trifluoride at −78 °C gave the hypervalent $ArBrF_2$ **323** and subsequent exchange with $CF_3SO_2NH_2$ gave the aryliminobromane **324** (Scheme 3.4).[251]



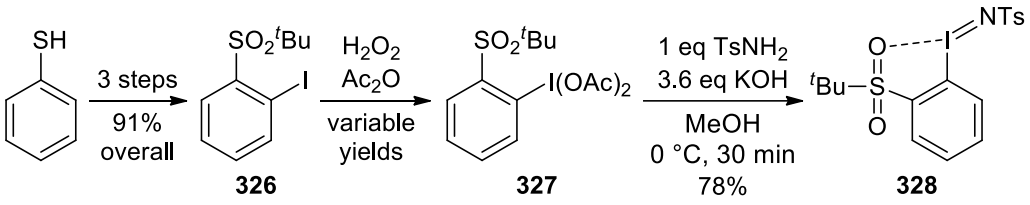
Scheme 3.4. Ochiai *et al.*'s preparation of a soluble aryliminobromane **324**.

Interestingly, the aryliminobromane **324** was capable of aziridinating a wide variety of alkenes without any metal catalysis at room temperature (Scheme 3.5). Good yields were obtained with both aliphatic and styrenic alkenes across a range of substitution patterns.



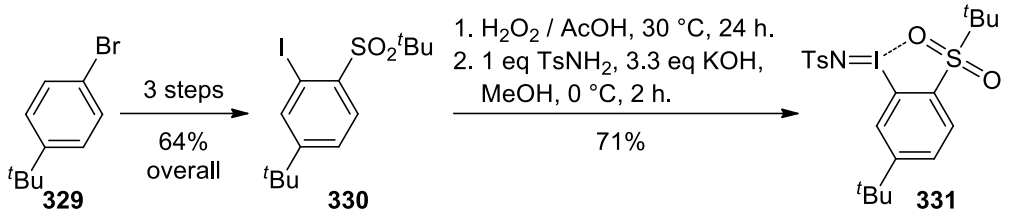
Scheme 3.5. Ochiai *et al.*'s aziridination of alkenes with aryliminobromane **324**.

Starting from thiophenol (Scheme 3.6), Protasiewicz *et al.* prepared an *o-tert*-butylsulfonylphenyliminoiodane **328** which had increased solubility relative to PhI=NTs due to the oxygen of the sulfone coordinating to the iodine centre.[252]



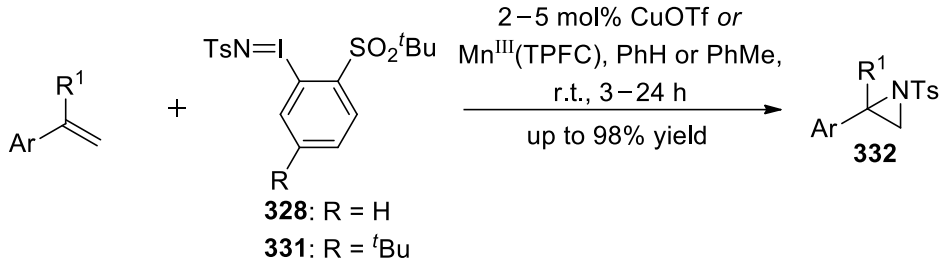
Scheme 3.6. Protasiewicz *et al.*'s synthesis of a soluble derivative of PhI=NTs.

Protasiewicz *et al.* also prepared another soluble aryliminoiodane from 4-*tert*-butylbromo benzene (**329**) (Scheme 3.7).[253] In this case, the intermediate diacetate was not isolated.



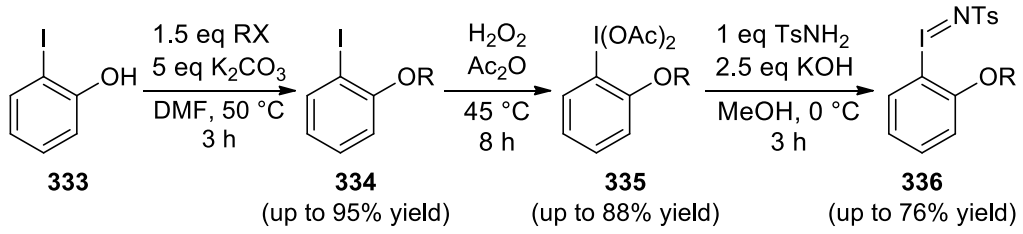
Scheme 3.7. Protasiewicz *et al.*'s synthesis of a soluble derivative of PhI=NTs.

Protasiewicz *et al.*'s soluble aryliminoiodanes **328** and **331** were able to aziridinate a range of aromatic alkenes using transition metal catalysts such as CuOTf and Mn^{III}(TPFC) (Scheme 3.8).[252-254] Both these aryliminoiodanes **328** and **331** gave similar yields, and could be run with either the aryliminoiodane or alkene as the limiting reagent.



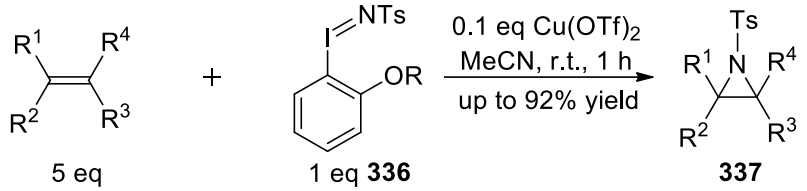
Scheme 3.8. Aziridinations with Protasiewicz *et al.*'s soluble aryliminoiodanes.

Yoshimura *et al.* prepared a range of soluble *o*-alkoxyphenyliminoiodanes, starting from 2-iodophenol (**333**) (Scheme 3.9).[255] Again, the oxygen atom in these soluble *o*-alkoxyphenyliminoiodanes contributed to the solubility of the molecules by coordinating to the iodine centre.



Scheme 3.9. Yoshimura *et al.*'s soluble *o*-alkoxyphenyliminoiodanes.

Yoshimura reported the $Cu(OTf)_2$ catalysed aziridination of a variety of both aromatic and aliphatic alkenes using these *o*-alkoxyphenyliminoiodanes in moderate to high yields (Scheme 3.10). Interestingly, they reported that their *o*-alkoxyphenyliminoiodanes were more reactive compared to Protasiewicz *et al.*'s soluble aryliminoiodanes.

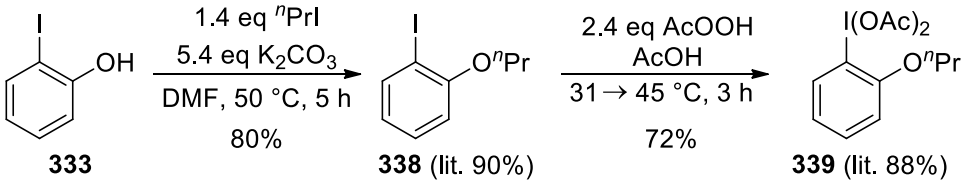


Scheme 3.10. Aziridination of alkenes with *o*-alkoxyphenyliminoiodanes.

3.3 Synthesis of *o*-propoxyaryliminoiodanes

As the synthesis of Ochiai *et al.*'s soluble aryliminobromane required special precautions due to the highly corrosive bromine trifluoride (BrF_3), and Protasiewicz *et al.*'s soluble aryliminoiodanes required many steps to synthesize, we decided to investigate use of Yoshimura *et al.*'s *o*-alkoxyphenyliminoiodanes in flow aziridinations. Not only was their synthesis straightforward, these aryliminioiodanes were reported to be highly reactive.

2-Iodophenol (**333**) was alkylated with 1-iodopropane to give 1-iodo-2-propoxybenzene (**338**) (Scheme 3.11). We chose to synthesize the *n*-propoxy derivative as Yoshimura *et al.* reported the best yields in aziridinations with the aryliminoiodane derived from it.



Scheme 3.11. Synthesis of $ArI(OAc)_2$ **339** from 2-iodophenol.

ArI **338** was then oxidized with commercially available 39% AcOOH in AcOH to give ArI(OAc)$_2$ **339**. The use of H_2O_2 / Ac_2O as reported in Yoshimura *et al.*'s original procedure was avoided as it was potentially more hazardous;[256] this change led to a small reduction in yield. We managed to grow a single crystal of ArI(OAc)$_2$ **339**, which confirms its structure (Figure 3.1); while Yoshimura *et al.* had reported the X- ray crystal structures of the other derivatives, they did not report one for **339**.

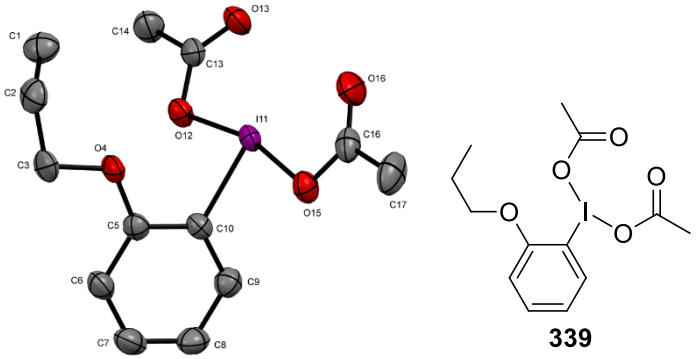
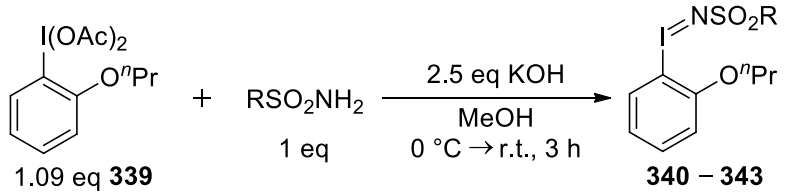
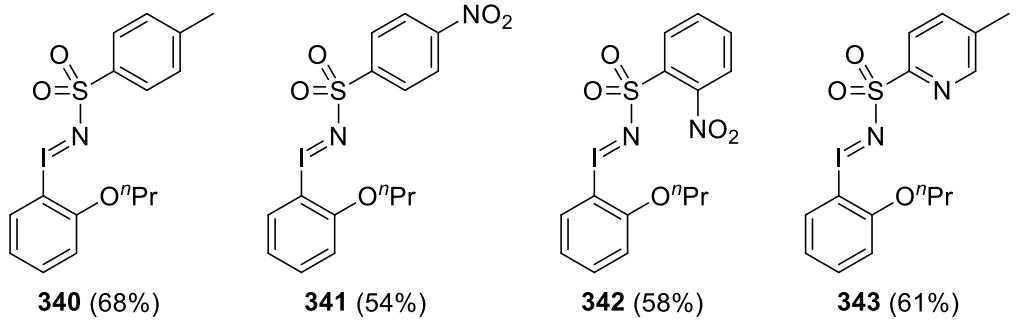


Figure 3.1. X-ray crystal structure of ArI(OAc)$_2$ **339**.

ArI(OAc)$_2$ **339** was reacted with a variety of sulfonamides RSO_2NH_2 to give a range of aryliminoiodanes ArI=NSO$_2$R **340** – **343** (Scheme 3.12). **340** was previously synthesized by Yoshimura *et al.*, but **341** – **343** are novel compounds.





Scheme 3.12. Synthesis of ArI=NSO$_2$R **340** – **343** from ArI(OAc)$_2$ **339**.

Aryliminoiodanes **341** – **343** bear *N*-sulfonyl groups which should be easier to remove than tosyl groups from nitrogen.[197, 257] The structure of **343** was confirmed by X-ray crystallography (Figure 3.2).

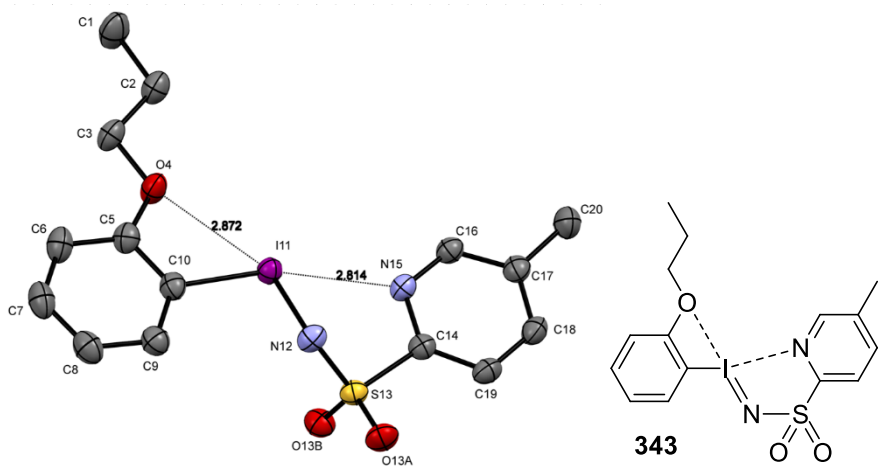
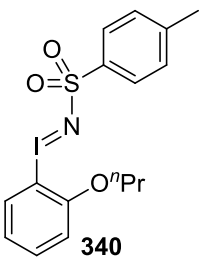
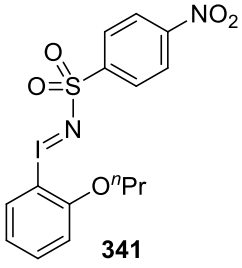
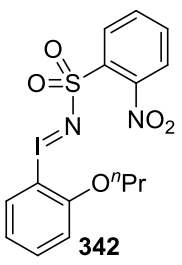
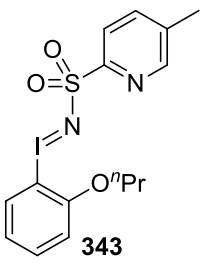


Figure 3.2. X-ray crystal structure of **343**.

PhI=NTs is insoluble in most organic solvents due to strong secondary intermolecular I···N interactions that gives rise to a polymeric structure.[258-261] Other than **341** which was only slightly soluble in $CHCl_3$, all the iminioiodanes proved to be very soluble (Table 3.1). This is due to the interaction between the iodine centre and the alkoxy oxygen, which disrupts intermolecular interactions. The solubility of **343** is further enhanced by the additional intramolecular interaction between the pyridine nitrogen and the iodine centre.

Table 3.1. Solubilities of the aryliminoiodanes **340** – **343**.

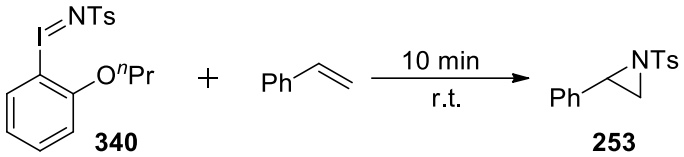
			
340	**341**	**342**	**343**
250 mg cm^{-3} (CH_2Cl_2)	5 mg cm^{-3} ($CHCl_3$)	22 mg cm^{-3} (CH_2Cl_2)	270 mg cm^{-3} (CH_2Cl_2)

3.4 Optimization of conditions for aziridination of styrene with 340

Our studies began with an investigation into the aziridination of styrene with ArI=NTs **340**. The procedure reported by Yoshimura *et al.* involved use of $Cu(OTf)_2$ in a minimum volume of acetonitrile.[255] However, this was found to be unsuitable for adapting to flow, as **340** has a low solubility in acetonitrile. Trial reactions were run under a variety of conditions and monitored by ^1H NMR (Table 3.2).

It was found that while the aziridination did not work in the absence of acetonitrile, **340** could first be dissolved in CH_2Cl_2 before adding to a solution of styrene and catalyst in CD_3CN. In the absence of catalyst, the aziridination did not work (entry 1). Instead, **340** decomposed to give the sulfonamide, with about 10% of $TsNH_2$ formed (<90% **340** remaining) after 1 hour.

Table 3.2. Optimization of conditions for aziridination of styrene by **340**.



340 **253**

Entry	Catalyst (eq)	Styrene (eq)	Conversion[a] (%)
1	–	10	0
2	$Cu(OTf)_2$ (0.1 eq)	10	76
3	**$(pyr)_4Cu(OTf)_2$ (0.1 eq)**	**10**	**85**
4	$(pyr)_4Cu(OTf)_2$ (0.1 eq)	2	63
5	$(pyr)_4Cu(OTf)_2$ (0.1 eq)	5	79
6	$(pyr)_4Cu(OTf)_2$ (0.05 eq)	10	61
7	$(pyr)_4Cu(OTf)_2$ (0.2 eq)	10	86

[a] Catalyst and styrene were dissolved in CD_3CN; 1 eq of **340** was dissolved in CH_2Cl_2; the two solutions were mixed in a NMR tube; conversion was determined after 10 min by ^1H NMR spectroscopy.

$Cu(OTf)_2$ (0.1 eq) catalyzed the aziridination of styrene with **340** efficiently (entry 2), but $(pyr)_4Cu(OTf)_2$ proved even better (entry 3). The optimum number of equivalents of styrene was 10 eq (entry 3), as decreasing it led to lower conversions (entries 4 and 5). Decreasing the number of equivalents of $(pyr)_4Cu(OTf)_2$ led to lower conversions (entry 6) but increasing it led to little improvement (entry 7). The optimized conditions for the aziridination of styrene with ArI=NTs **340** was 0.1 eq $(pyr)_4Cu(OTf)_2$, and 10 eq styrene (entry 3).

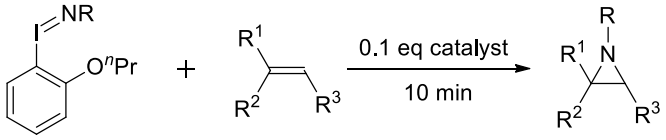
3.5 Investigation into scope of alkene aziridination with aryliminoiodanes.

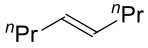
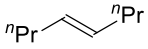
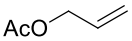
With suitable conditions for the ArI=NTs **340** aziridination of styrene identified, we decided to test the aziridination of a range of alkenes with aryliminoiodanes **340**, **342**, and **343** again under batch conditions before moving to flow (Table 3.3).

When styrene was aziridinated with aryliminoiodanes **340**, **342** and **343**, ^{1}H NMR indicated the corresponding aziridines were produced with good conversions within 10 min (entries 1 – 3). As the literature with PhI=NTs indicated that styrenic substrates tended to have similar reactivities, we focused our studies on aliphatic alkenes, which tended to be much more difficult to aziridinate.[262-264]

Unfortunately, the results for the aziridination of aliphatic alkenes with aryliminoiodanes **340**, **342** and **343** under our conditions were not especially encouraging. Our data revealed that **340** and **342** can aziridinate the extremely reactive norbornene within 10 min (entries 4 and 5), but **343** was ineffective (entry 6). This led us to focus our efforts into the aziridination of aliphatic alkenes with iminoiodanes **340** and **342**.

Table 3.3. Batch aziridination of alkenes.



Entry	Alkene (eq)	R	Catalyst	Conversion
1	 (10 eq)	Ts	$(pyr)_4Cu(OTf)_2$	84%; reaction complete.
2	 (10 eq)	oNs	$(pyr)_4Cu(OTf)_2$	81%; reaction complete.
3	 (10 eq)	Xs[a]	$(pyr)_4Cu(OTf)_2$	82%; reaction complete.
4	 (10 eq)	Ts	$(pyr)_4Cu(OTf)_2$	73%; reaction complete.
5	 (10 eq)	oNs	$(pyr)_4Cu(OTf)_2$	69%; reaction complete.
6	 (10 eq)	Xs[a]	$(pyr)_4Cu(OTf)_2$	No reaction; ArI=NXs **343** slowly decomposes.
7	 (10 eq)	Ts	$(pyr)_4Cu(OTf)_2$	No reaction; ArI=NTs **340** slowly decomposes.
8	 (10 eq)	Ts	$Cu(OTf)_2$	No reaction; ArI=NTs **340** slowly decomposes.
9	 (10 eq)	oNs	$(pyr)_4Cu(OTf)_2$	35% after 10 min, with ArI=NoNs **342** remaining.
10	 (10 eq)	oNs	$Cu(OTf)_2$	24% after 10 min, with ArI=NoNs **342** remaining.
11	 (20 eq)	oNs	$(pyr)_4Cu(OTf)_2$	47%; reaction complete.
12	 (10 eq)	oNs	$(pyr)_4Cu(OTf)_2$	6% after 10 min, with ArI=NoNs **342** remaining.
13	 (20 eq)	oNs	$(pyr)_4Cu(OTf)_2$	11% after 10 min, with ArI=NoNs **342** remaining.
14	 (20 eq)	oNs	$(pyr)_4Cu(OTf)_2$	No reaction; ArI=NoNs **342** slowly decomposes.
15	 (20 eq)	oNs	$(pyr)_4Cu(OTf)_2$	No reaction; ArI=NoNs **342** slowly decomposes.

[a] Xs is 2-sulfonyl-5-methylpyridine. [b] Alkene and 0.1 eq catalyst were dissolved in CD_3CN; arylimimoiodane was dissolved in CH_2Cl_2, and the two solutions mixed. [c] Measured by ^1H NMR spectroscopy.

When the aziridination of cycloheptene with **340** was examined, there was no evidence for production of aziridine (entry 7). As Yoshimura *et al.* reported that cycloheptene could be aziridinated with ArI=NTs **340**, we wondered if this could be because $Cu(OTf)_2$ was better than $(pyr)_4Cu(OTf)_2$ at aziridinating aliphatic alkenes. Unfortunately, the aziridination still did not work with $Cu(OTf)_2$ as catalyst under our conditions (entry 8).

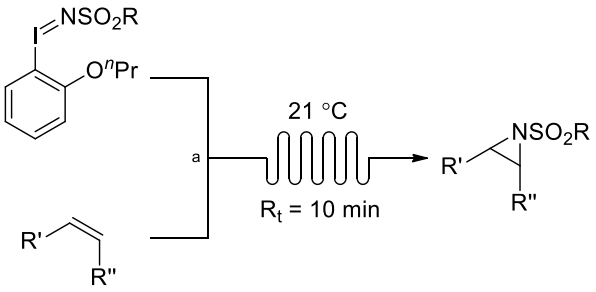
However, the aziridination of cycloheptene with ArI=N^{o}Ns **342** was more successful, with NMR indicating 35% conversion after 10 min with ArI=N^{o}Ns **342** remaining (entry 9). When the number of equivalents of cycloheptene was increased to 20 equivalents (entry 11), the aziridination was complete, with 47% conversion into aziridine. Aziridination of cycloheptene with $Cu(OTf)_2$ was less effective (entry 10).

While NMR indicated traces of aziridine were formed in the aziridination of *trans*-4-octene, we were unable to get acceptable yields even by increasing the number of equivalents of alkene (entries 12 and 13). The aziridination of 1-octene and allylacetate were unsuccessful using 20 equivalents of alkene with ArI=N^{o}Ns **342** (entries 14 and 15).

3.6 Continuous flow aziridination of alkenes

Having identified the scope of these aziridinations in batch, we next applied the optimized conditions to the continuous flow aziridination of substituted styrenes, norbornene, and cycloheptene (Table 3.4). A modification of the glass micro-reactor described in Chapter 2, Figure 2.7, was used; input C was blocked off to convert the three-input microreactor into a two-input microreactor.

Table 3.4. Aziridination of alkenes under continuous flow.



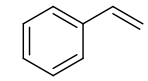
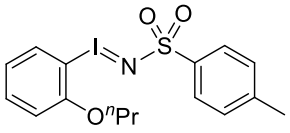
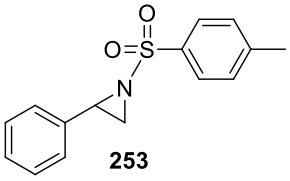
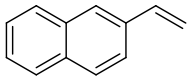
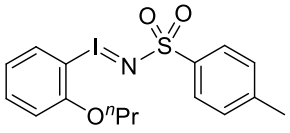
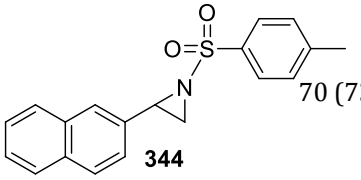
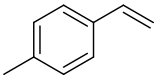
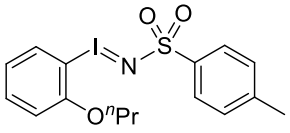
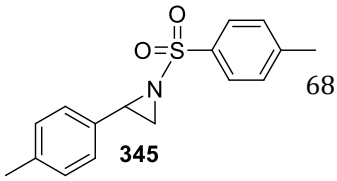
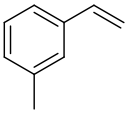
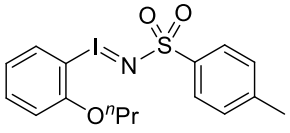
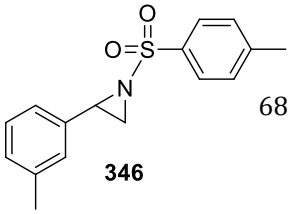
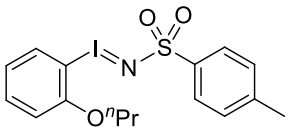
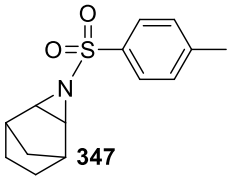
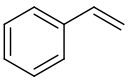
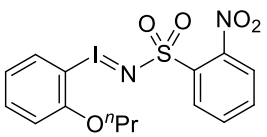
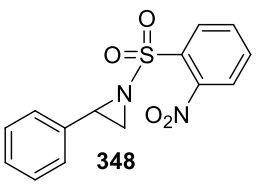
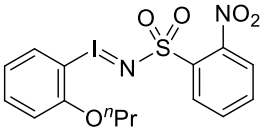
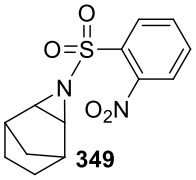
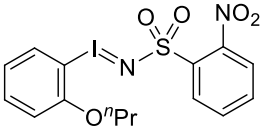
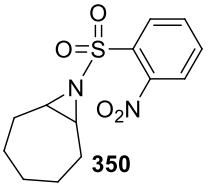
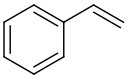
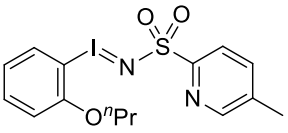
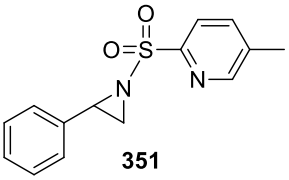
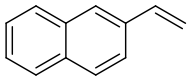
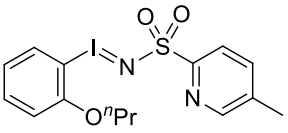
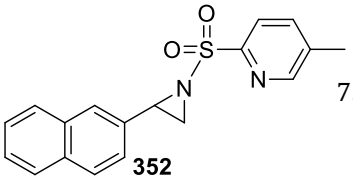
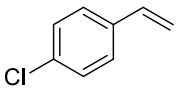
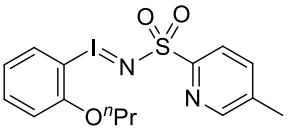
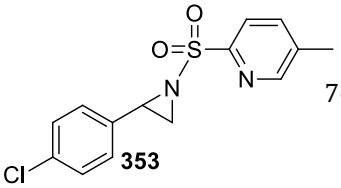
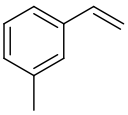
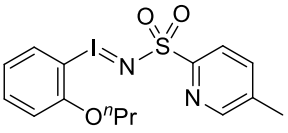
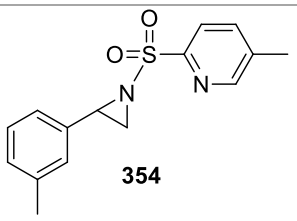
Entry	Alkene	ArI=NSO$_2$R	Aziridine	Yield[b] (%)
1		 **340**	 **253**	82
2		 **340**	 **344**	70 (73[c])
3		 **340**	 **345**	68
4		 **340**	 **346**	68 (68[c])
5		 **340**	 **347**	71
6		 **342**	 **348**	77

Table 3.4. Aziridination of alkenes under continuous flow (continued).

Entry	Alkene	ArI=NSO$_2$R	Aziridine	Yield[b] (%)
7		 **342**	 **349**	70
8		 **342**	 **350**	46[d]
9		 **343**	 **351**	79
10		 **343**	 **352**	73
11		 **343**	 **353**	76
12		 **343**	 **354**	82

[a] 1 eq ArI=NSO$_2$R in CH_2Cl_2; 10 eq alkene and 0.1 eq $(pyr)_4Cu(OTf)_2$ in MeCN; the two-input microreactor was used. [b] Isolated yields after chromatography. [c] The PTFE tubing flow reactor was used. [d] 20 eq of cycloheptene was used.

A custom built flow reactor constructed out of PTFE tubing could also be used instead of the glass microreactor, with similar yields obtained. A residence time of R_t = 10 min was appropriate, as prior NMR studies indicated that the reaction was complete in this timeframe. ArI=^{p}Ns **341** was not soluble enough to be used for aziridinations under continuous flow.

ArI=NTs **340** was capable of aziridinating styrene (entry 1), 2-vinylnaphthalene (entry 2), 4-methylstyrene (entry 3), 3-methylstyrene (entry 4) and norbornene (entry 5) in good yields; all the products from the aziridination with **340** could easily be isolated by column chromatography without decomposition.

Unfortunately for ArI=N^{o}Ns **342**, we were unable to isolate the aziridines derived from aromatic alkenes other than **348** (entry 6). ^{1}H NMR of these reaction mixtures indicated the formation of aziridine, but attempts to isolate and purify the aziridines by column chromatography were not successful. This leads us to conclude these aziridines are quite reactive, being unstable to column chromatography. However, this proved to be useful for the telescoped ring opening processes described in section 3.7, where these reactive aziridines derived from ArI=N^{o}Ns **342** and aromatic alkenes were directly ring opened in a cascade sequence. However, the aziridines derived from ArI=N^{o}Ns **342** and norbornene (entry 7) or cycloheptene (entry 8), were stable enough to be isolated by column chromatography.

Aryliminoiodane **343** was capable of aziridinating aromatic alkenes effectively, and the aziridines derived from it could be isolated without decomposition in good yields (entries 9 – 12).

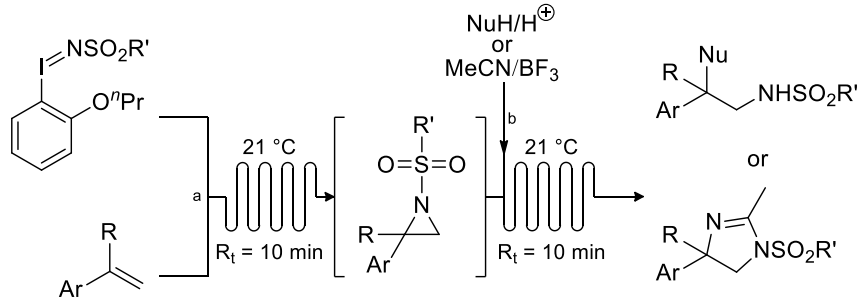
Through the use of aryliminoiodanes **340**, **342**, and **343**, we have successfully achieved the flow aziridination of a range of alkenes in good yields (46 – 82%), through application of copper catalysis. Our flow processes are faster than those reported for related batch processes,[58, 255] and proceed under very mild conditions. We think it is a significant advance on other flow aziridinations, being operationally straightforward, quick and rather general.

3.7 Aziridination of alkenes and subsequent cascade reactions

Next, we set about ascertaining if telescoped reactions could be undertaken in which the aziridine generated from the alkene could be directly ring opened without recourse to handling or isolation. We anticipated that this approach would be more general than our studies detailed in Chapter 2, as the alkene starting material and the iodoarene by-product would be rather inert and should not interfere in the subsequent telescoped step. This would be extremely useful in the case of aziridination of styrene derivatives with ArI=N^{o}Ns **342** as the *o*-nosyl protecting group makes the aziridine extremely reactive toward ring openings.

For these cascade reactions, we used a custom built flow reactor constructed out of PTFE tubing; details of its construction are given in section 6.15. We used a residence time of 10 min for both the aziridination and ring opening steps, with the temperature at 21 °C. 5 equivalents of alkene were used in the telescoped process in order to reduce side reactions such as the polymerization by the acid catalyst (1.5 – 5.1 eq). Further optimization of the cascade process was not carried out as the reaction conditions were mild and rapid. Using these telescoped reactions, nucleophiles such as methanol, ethanol, benzyl alcohol, hydrogen chloride and acetonitrile could be used to ring open the aziridines (Table 3.5).

Table 3.5. Aziridination of alkenes and subsequent ring opening in flow.



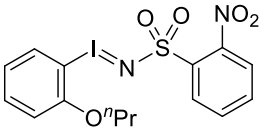
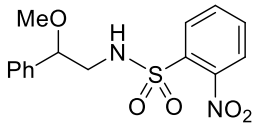
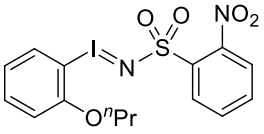
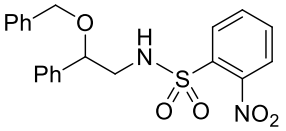
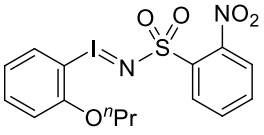
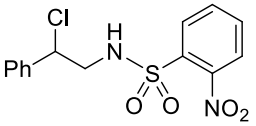
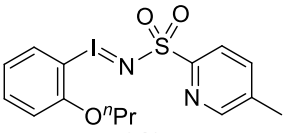
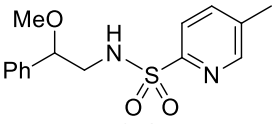
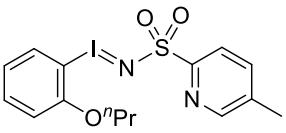
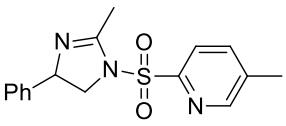
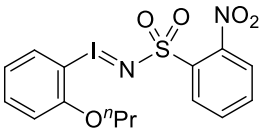
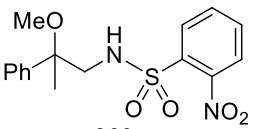
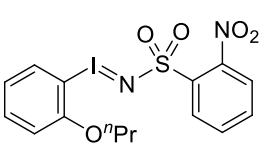
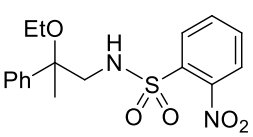
Entry	Alkene	ArI=NSO$_2$R	Nucleophile[b]	Product	Yield[c] (%)
1		 **342**	MeOH	 **355**	73
2		 **342**	BnOH	 **356**	55
3		 **342**	HCl	 **357**	55
4		 **343**	MeOH	 **358**	64
5		 **343**	MeCN	 **359**	71
6		 **342**	MeOH	 **360**	67
7		 **342**	EtOH	 **361**	56

Table 3.5. Aziridination of alkenes and subsequent ring opening in flow (continued).

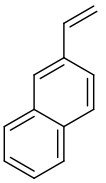
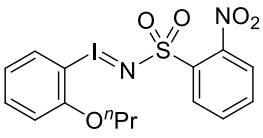
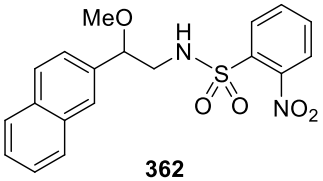
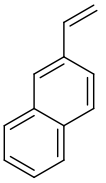
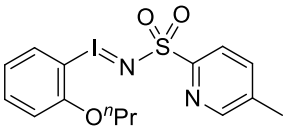
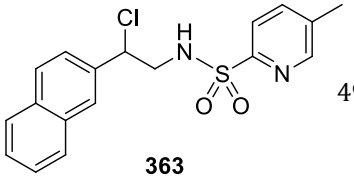
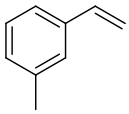
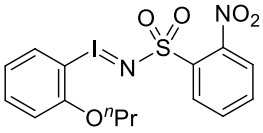
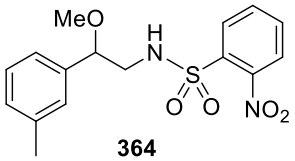
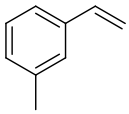
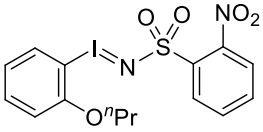
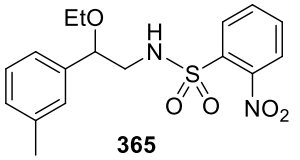
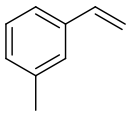
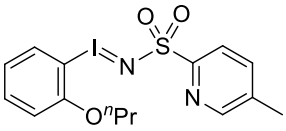
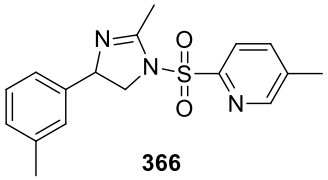
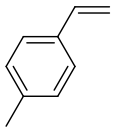
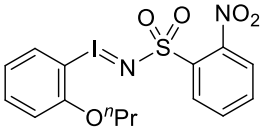
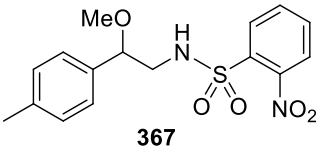
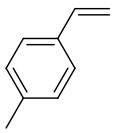
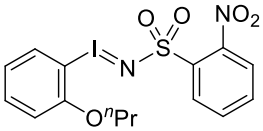
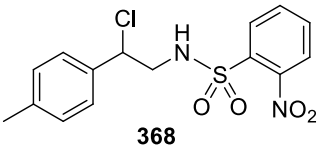
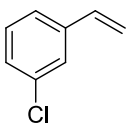
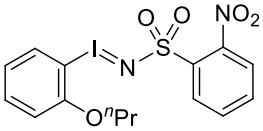
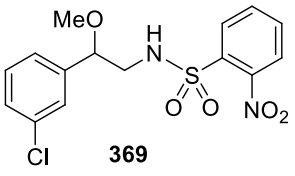
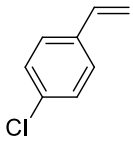
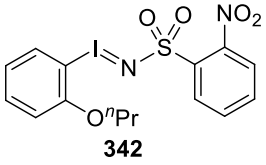
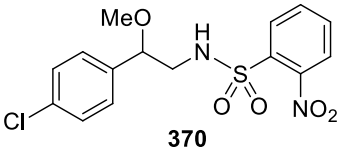
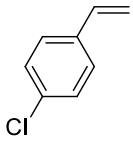
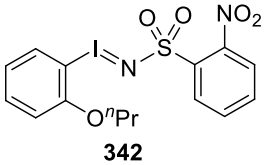
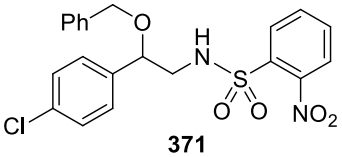
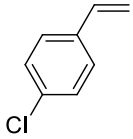
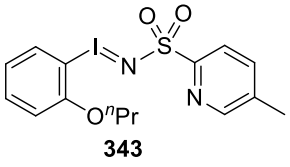
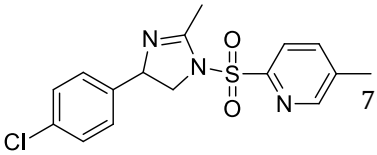
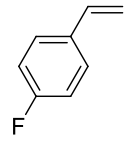
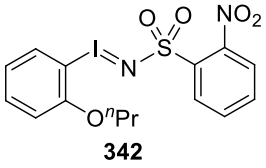
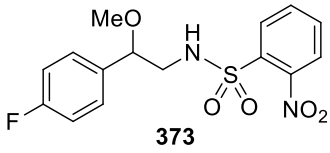
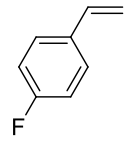
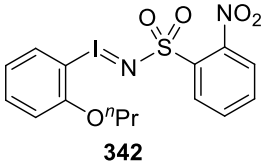
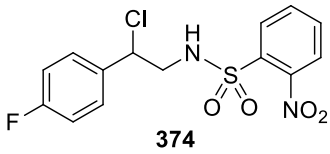
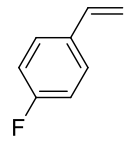
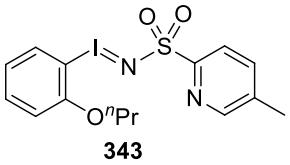
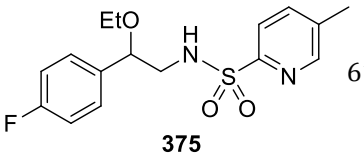
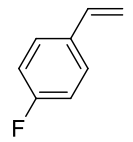
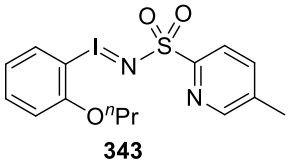
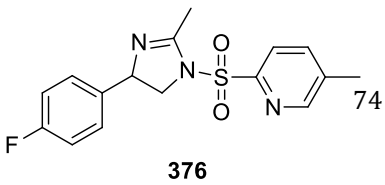
Entry	Alkene	ArI=NSO$_2$R	Nucleophile[b]	Product	Yield[c] (%)
8		 **342**	MeOH	 **362**	71
9		 **343**	HCl	 **363**	49
10		 **342**	MeOH	 **364**	76
11		 **342**	EtOH	 **365**	78
12		 **343**	MeCN	 **366**	77
13		 **342**	MeOH	 **367**	73
14		 **342**	HCl	 **368**	58
15		 **342**	MeOH	 **369**	48

Table 3.5. Aziridination of alkenes and subsequent ring opening in flow (continued).

Entry	Alkene	ArI=NSO$_2$R	Nucleophile[b]	Product	Yield[c] (%)
16		 **342**	MeOH	 **370**	79
17		 **342**	BnOH	 **371**	61
18		 **343**	MeCN	 **372**	70
19		 **342**	MeOH	 **373**	77
20		 **342**	HCl	 **374**	52
21		 **343**	EtOH	 **375**	61
22		 **343**	MeCN	 **376**	74

[a] 1 eq ArI=NSO$_2$R in CH_2Cl_2; 5 eq alkene and 0.1 eq $(pyr)_4Cu(OTf)_2$ in MeCN. [b] H_2SO_4 in MeOH or EtOH; MsOH in BnOH; HCl in Et_2O/CH_2Cl_2; BF_3 in MeCN. [c] Isolated yields after chromatography.

Alcohols generally ring opened the aziridines derived from ArI=N^{o}Ns **342** in the telescoped flow process in high yields (entries 1, 2, 6 – 8, 10, 11, 13, 15 – 17, 19). The telescoped alcohol ring openings of aziridines derived from **343** had moderate yields (entries 4 and 21), perhaps because the pyridine nitrogen competes for the protonation, disfavouring activation of the aziridine nitrogen. Chloride ring openings gave moderate yields with the aziridines formed from both aryliminoiodanes **342** and **343** (entries 3, 9, 14, 20).

Formal cycloadditions with acetonitrile were possible with *in situ* aziridines derived from **343** in good yields in general (entries 5, 12, 18, 22). Attempts to do the same chemistry using ArI=N^{o}Ns **342** were unsuccessful, possibly due to the imidazolines being more susceptible to hydrolysis due to the *o*-nosyl group, although this was not examined further. When nitriles other than MeCN were used as the solvent in the second step of the telescoped process to try and vary the *C*-2 substituent, a mixture of imidazolines was obtained arising from presence of MeCN. Replacing acetonitrile with other nitriles in the initial aziridination step caused the aziridination to fail.

The *N*-tosyl aziridines formed *in situ* from ArI=NTs **340** were not sufficiently reactive to undergo alcohol ring openings under our telescoped process (21 °C, R_t = 10 min, 1.5 – 5.1 eq H_2SO_4). Increasing the residence time for the ring opening step to 20 min did not lead to any improvement. Increasing the number of equivalents of H_2SO_4 (more than 20 eq) such that there was no more *N*-tosyl aziridine detected did not work either, as no ring opened product could be isolated. Increasing the temperature of the cascade process to 30 °C caused problems due to the boiling of CH_2Cl_2.

When the cascade sequence involving BF_3/MeCN was tried with aziridines derived from ArI=NTs **340**, no imidazolines were isolated.

A range of nitrogen nucleophiles such as ammonia in methanol, hydroxylamine, benzylamine, dimethylamine, diethylamine, and aniline were tried in the cascade process with ArI=N^{o}Ns **342** and ArI=NSO_2R **343**, but it was not possible to isolate any ring opened product from the reaction mixture.

Complete regioselectivity was observed in all products by analysis of the crude ^{1}H NMR spectra. In the case of the alcohol ring openings, attack of the alcohol at the benzylic position was confirmed by HMBC three-bond couplings, as described in section 2.8. Alcohol and chloride ring openings showed COSY three-bond couplings between the N*H* and NCH_2. Additionally, the X-ray crystal structure of **363** provided further evidence for the observed regiochemistry (Figure 3.3).

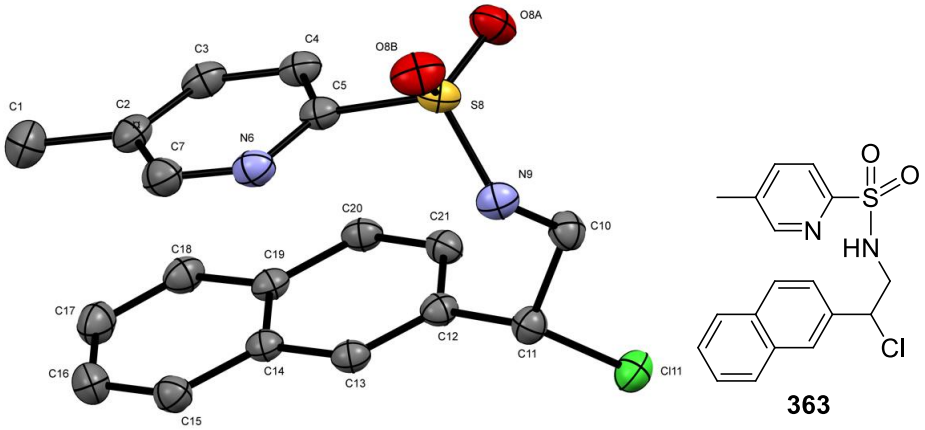


Figure 3.3. X-ray crystal structure of **363**.

In the case of formal [3+2] cycloadducts with acetonitrile, the regioselectivity proposed is consistent with the NMR data presented in section 2.9. In particular, the ^{1}H NMR spectra of products **359**, **366**, **372** and **376** had characteristic ArC*H* peaks at around 5 ppm and two signals for CH*H* and C*H*H at 3 – 4 ppm.

3.8 Conclusions

We have synthesized a series of aryliminoiodanes **340** – **343** in 3 steps from 2-iodophenol. Of these, ArI=NTs **340** is known, while ArI=NSO_2R **341** – **343** are novel. Using these aryliminoiodanes, we identified efficient conditions for the aziridination of a wide range of alkenes. The high solubility of these aryliminoiodanes enabled them to be successfully used in flow for the first time, and 12 aziridines were synthesized under continuous flow with good yields.

The mild and clean conditions for these aziridinations with few side products enabled them to be combined with further ring opening or formal cycloadditions. A variety of alkenes were aziridinated and the *in situ* aziridines directly reacted with various nucleophiles, in telescoped flow processes. This telescoped flow process enabled the synthesis of a range of nitrogen containing molecules (22 examples) directly from the alkene, without having to isolate and purify the intermediate aziridine. This is very useful in cases where the aziridines formed are highly reactive and difficult to isolate, such as 2-aryl *N*-^{o}Ns aziridines, or are potentially hazardous.

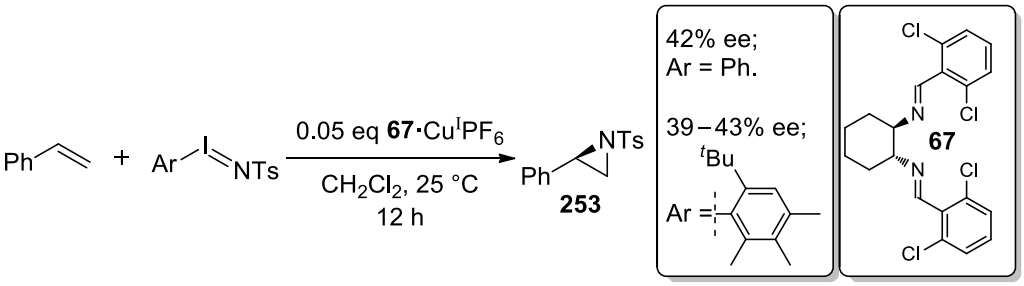
The work discussed in this chapter was published in Organic Letters in 2016.[265]

Chapter 4: Stereocontrolled Aziridinations with *N*-tosyl Aryliminoiodanes

4.1 Introduction

The use of phenyliminoiodanes PhI=NSO_2R in asymmetric aziridinations with transition metal catalysts and chiral ligands has been thoroughly investigated over the past two decades[60-63, 266] as detailed in Chapter 1.

Whilst there have been a number of studies exploring variation in the R group of PhI=NSO_2R in asymmetric aziridinations,[59, 267] fewer studies have examined the impact of changing the aryl group of *N*-tosyl aryliminoiodanes ArI=NTs. This is because it is widely believed that the nitrene source is fully dissociated from the iodoarene in the transition state.[268-269] One study by Jacobsen *et al.* showed that ee was unchanged if the aryl group was changed (Scheme 4.1).[270]



Scheme 4.1. Asymmetric aziridination with different *N*-tosyl aryliminoiodanes.

Evidence for a fully dissociated nitrene intermediate was provided by Au *et al.,* in which the *bis*(tosyl)imidoruthenium (VI) porphyrin complex **377** was shown to effect the stoichiometric aziridination of various alkenes.[268-269]

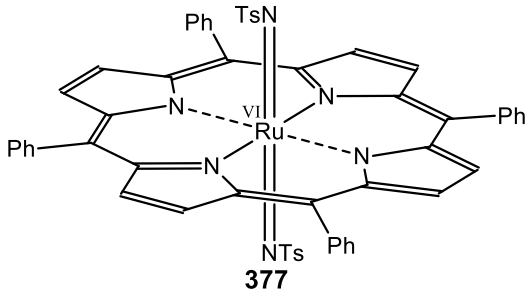
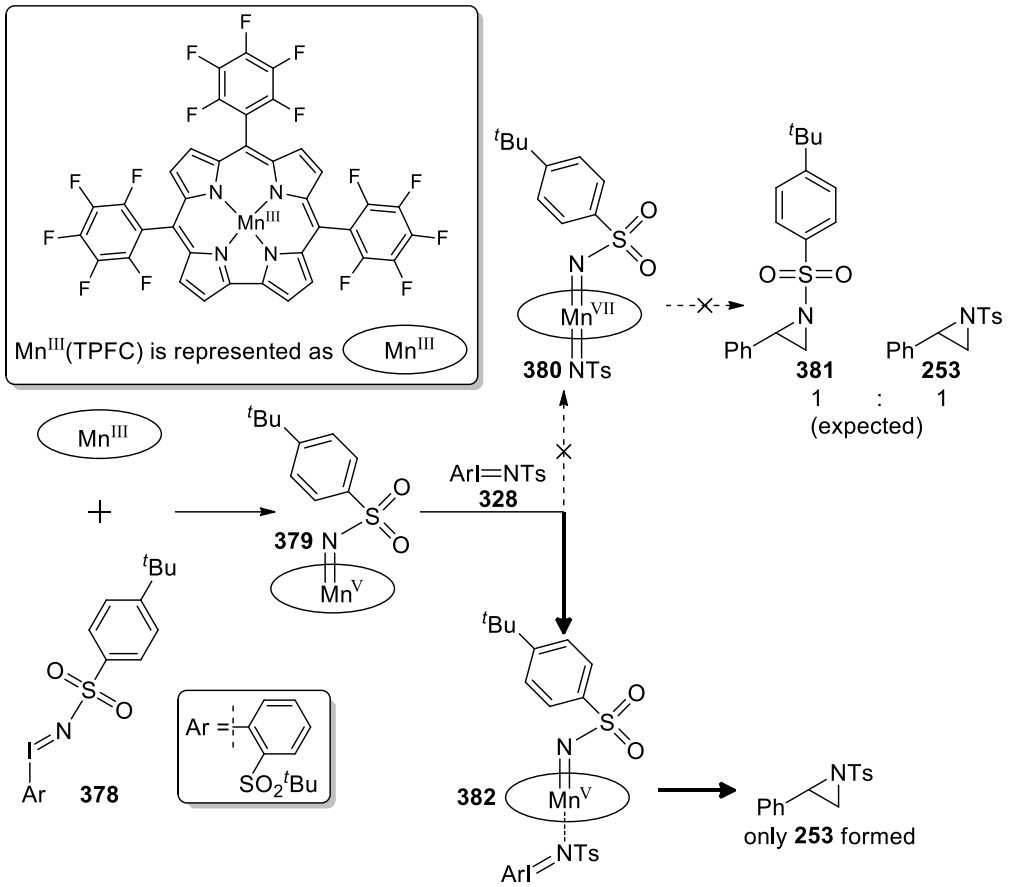


Figure 4.1. *Bis*(tosyl)imidoruthenium (VI) porphyrin complex **377**.

In 2006, Zdilla *et al.* reported that in aziridinations catalysed by Mn^{III}(TPFC), the Mn^{III}(nitrenoid) complex was still associated with the iodoarene, as evidenced by double labelling experiments (Scheme 4.2).[254] Mn^{III}(TPFC) was reacted with aryliminoiodane **378** to give the Mn^{V}(imido) complex **379**. **379** was not able to act as a stoichiometric reagent in the aziridination of styrene, but was able to catalyse aziridination of styrene with aryliminoiodanes. **379** was reacted with a different aryliminoiodane ArI=NTs **328**, and then reacted with styrene, giving only aziridine **253**. This strongly suggests that the nitrenoid intermediate **382** was still bound to the iodoarene. If the iodoarene was fully dissociated, as in **380**, a 1:1 mixture of **381** and **253** would have been expected. Crucially, when the order of arylimino-iodanes **328** and **378** was switched, only **381** was formed, which further confirms that the iodoarene is still attached to the nitrenoid during aziridination.

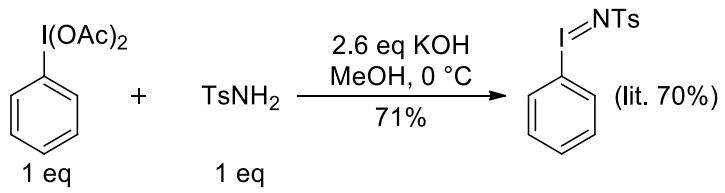


Scheme 4.2 Zdilla *et al.*'s double labelling experiment.

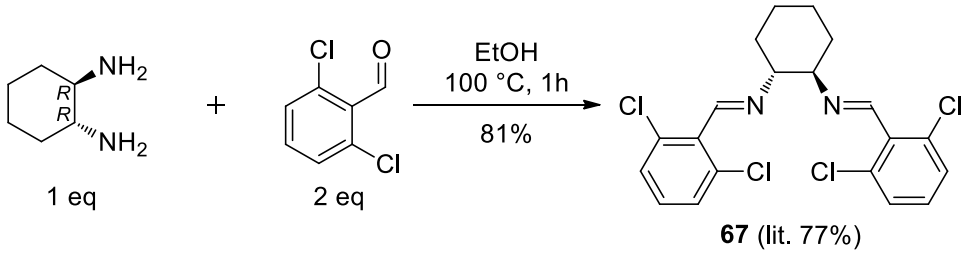
Thus, with some evidence that the iodoarene is still attached to the nitrenoid in Mn^{III}(TPFC) catalysed aziridinations, we were interested to see if the *o*-propoxy substituent of ArI=NTs **340** would lead to any difference in asymmetric or diastereoselective aziridinations compared to PhI=NTs. The increased solubility of ArI=NTs **340** compared with PhI=NTs might also have an impact in the selectivity of such stereocontrolled aziridinations.

4.2 Enantioselective aziridination of styrene

PhI=NTs was synthesized from $PhI(OAc)_2$ according to the published method (Scheme 4.3).[55] Jacobsen's chiral ligand **67** was synthesized from (*1R,2R*)-cyclohexane-1,2-diamine, using Jacobsen *et al.*'s procedure (Scheme 4.4).[60]



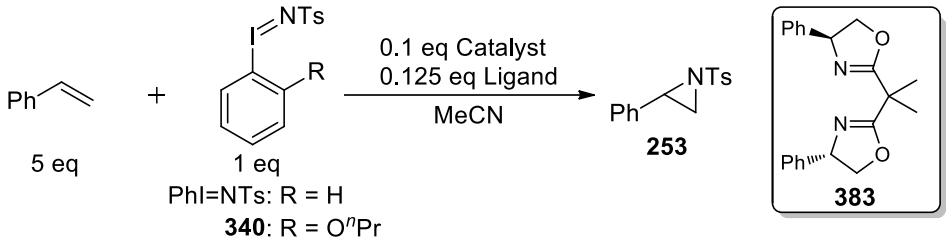
Scheme 4.3. Synthesis of PhI=NTs



Scheme 4.4. Synthesis of Jacobsen's chiral diimine ligand.

Using PhI=NTs, ArI=NTs **340**, Jacobsen's chiral diimine ligand **67**, and commercially available Evan's chiral *bis*(oxazoline) ligand **383**, the asymmetric aziridination of styrene was investigated under a range of different batch conditions (Table 4.1). Most of the reactions were run in acetonitrile as solvent. Enantiomeric excess (ee) was determined by chiral HPLC.[246]

Table 4.1. Investigation into enantioselective aziridinations with styrene.



Entry	ArI=NTs	Catalyst	Ligand	Temperature (°C)	Reaction time[a] (h)	Yield[b] and ee
1	PhI=NTs	$Cu(OTf)_2$	**383**	0	1.5	73%; 10% ee
2	PhI=NTs	**Cu(OTf)**	**383**	0	1.5	72%; 10% ee
3	**340**	$Cu(OTf)_2$	**383**	0	0.5	76%; 30% ee
4	**340**	**Cu(OTf)**	**383**	0	0.5	74%; 29% ee
5	**340**	$Cu(OTf)_2$	**383**	−40 → 0	2	54%; 30% ee
6[c]	PhI=NTs	$Cu(OTf)_2$	**383**	0	3	67%; 9% ee
7[c]	**340**	$Cu(OTf)_2$	**383**	0	1	68%; 9% ee
8	PhI=NTs	$Cu(OTf)_2$	**67**	0	2	77%; 38% ee
9	PhI=NTs	**Cu(OTf)**	**67**	0	2	75%; 37% ee
10	**340**	$Cu(OTf)_2$	**67**	0	0.5	73%; 37% ee
11	**340**	**Cu(OTf)**	**67**	0	0.5	75%; 37% ee

[a] Time taken for all the ArI=NTs to dissolve. [b] Isolated yield after chromatography. [c] Reaction was run in styrene as solvent.

Using Evan's chiral *bis*(oxazoline) ligand **383**, $Cu^{II}(OTf)_2$ and PhI=NTs at 0 °C, the reaction was complete within 1.5 h, with 73% yield and 10% ee (entry 1). Changing the catalyst from Cu^{II} to Cu^{I} did not make much difference to the rate, yield or enantioselectivity (entry 2). Changing the aryliminoiodane from PhI=NTs to ArI=NTs **340** increased the rate of reaction (complete within 0.5 h) with a similar yield, but the ee was increased to 30% (entry 3).

When Cu^{II} was changed to Cu^{I} with aryliminoiodane **340**, there was no significant change to rate, yield or ee (entry 4).

The lack of difference in asymmetric induction (ee) between Cu^{II} and Cu^{I} is consistent with the literature for asymmetric aziridinations suggesting the oxidation state of the copper is the same in the transition state.[62] However, the difference in ee between PhI=NTs and ArI=NTs **340** was encouraging, and suggests that the active nitrene species is at least partially bound to the iodoarene in the transition state. As the difference in ee was counter to the findings of Jacobsen *et al.*, albeit with different catalyst (Scheme 4.1), entries 1 and 3 were run multiple times, with ArI=NTs **340** giving a consistently higher ee (29 – 30%) compared to PhI=NTs (9 – 10%).

Unfortunately, attempts to improve the enantioselectivity were unsuccessful with $Cu(OTf)_2$ and Evans' *bis*(oxazoline) ligand **383**. Decreasing the temperature to −40 °C with ArI=NTs **340** caused the reaction to slow down drastically, and the aziridination only occurred upon warming to 0 °C, with a lower yield but similar ee (entry 5). Using styrene as solvent, slightly lower yields were obtained with both PhI=NTs and ArI=NTs **340**, but the ee for both iminoiodanes were now the same (9%) (entries 6 and 7). We were unable to achieve enantioselectivies as high as that reported in the literature with ligand **383** (lit. 63% ee).[59, 62] This might be due to trace contaminants in ligand **383** or copper catalysts.

However, when the chiral ligand was changed to Jacobsen's chiral diimine ligand **67**, similar yields and ee were obtained for both PhI=NTs and ArI=NTs **340** (entries 8 – 11). These results suggest that with Jacobsen's diimine ligand **67**, the iodoarene is completely dissociated from the active nitrene species. Jacobsen *et al.*[270] obtained 39 – 43% ee for the asymmetric aziridination of styrene with *N*-tosyl aryliminoiodanes, which is similar to the values we obtained (37 – 38%).

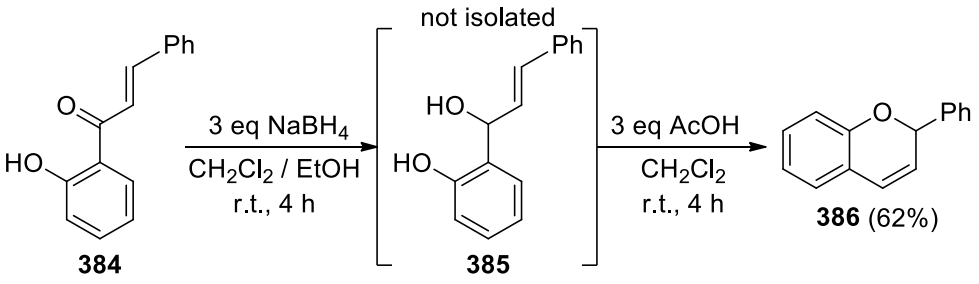
The initial results obtained with **383** are interesting from a mechanistic point of view, as copper-nitrene intermediates have been thought to be totally dissociated from the iodoarene species. Unfortunately, due to time constraints, we were unable to investigate other chiral ligands and transition metal catalysts to explore these findings further.

4.3 Diastereoselective aziridination of 2-phenyl-2*H*-chromene

As the copper catalyzed enantioselective aziridinations of styrene with PhI=NTs and ArI=NTs **340** were inconclusive, we decided to investigate diastereoselective aziridinations with Mn(TPFC). Zdilla *et al.* had shown that with Mn(TPFC), the iodoarene is still attached to the nitrene source.[254] It was hoped that by using an alkene with a chiral centre, aziridination would be favoured from the less hindered face of the alkene, and that interactions from the bulkier iodoarene in ArI=NTs **340** would enhance this selectivity. A further advantage of exploring diastereocontrol is that the catalyst system is more straightforward to assemble, with fewer experimental variables.

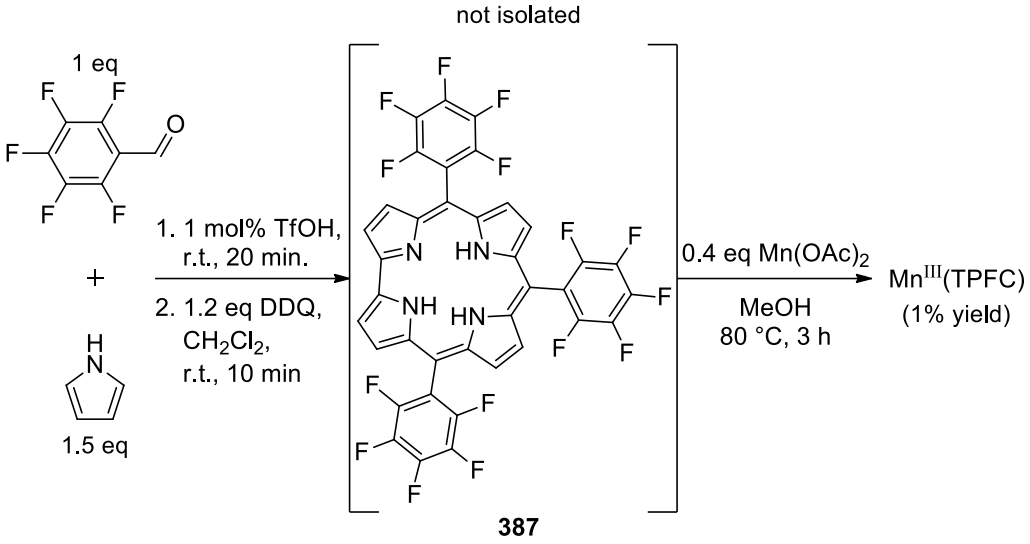
Mn(TPFC) is known to be an effective catalyst in the aziridination of aromatic but not aliphatic alkenes.[254] As there were not many reports on diastereoselective aziridinations of aromatic alkenes, we explored the literature on diastereoselective *epoxidations* of aromatic alkenes. Day *et al.* reported that various 2-substituted 2*H*-chromenes could be diastereoselectively epoxidized from the less hindered face.[271] Of the various 2*H*-chromenes epoxidized, 2-phenyl-2*H*-chromene was the most shelf-stable and straightforward to synthesize. Thus, we choose to investigate the diastereoselective aziridination of 2-phenyl-2*H*-chromene (**386**).

2-Phenyl-2*H*-chromene (**386**) was synthesized by adaptation of a literature method.[272] Chalcone **384** was reduced with $NaBH_4$ to give alcohol **385**, which was then immediately cyclized to give chromene **386** (Scheme 4.5).



Scheme 4.5. Synthesis of 2-phenyl-2*H*-chromene.

Mn(TPFC) was synthesized by a modification of a literature procedure.[273-275] Pentafluorobenzaldehyde and pyrrole were first reacted with TfOH and DDQ to give *tris*(pentafluorophenyl)corrole **387**, which was reacted directly with $Mn(OAc)_2$ to give Mn^{III}(TPFC) (Scheme 4.6).



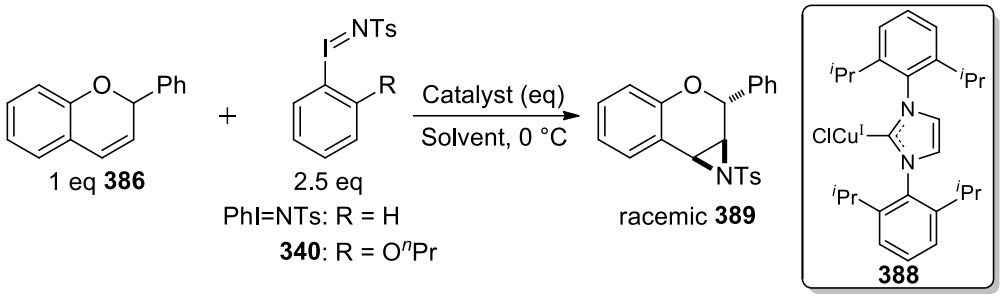
Scheme 4.6. Synthesis of Mn(TPFC).

A number of different conditions were examined for the aziridination of chromene **386** with PhI=NTs and ArI=NTs **340** (Table 4.2). Unfortunately, the highest yield was only 5%, and was obtained with $Cu(OTf)_2$ and PhI=NTs in acetonitrile (entry 1). The rest of the reaction mixture consisted of $TsNH_2$ and unidentifiable compounds.

Use of ArI=NTs **340** increased the rate of reaction but the yield was similar to PhI=NTs (entry 2). Lowering the temperature from 0 °C to −20 °C with ArI=NTs **340** caused the reaction to slow down and the yield to drop (entry 3). Unfortunately, it was not possible to accurately determine the diastereoselectivity of these reactions as the crude ^{1}H NMR spectra were extremely complex.

When 0.01 eq of Mn(TPFC) was used, no aziridine was formed with either PhI=NTs (entry 4) or ArI=NTs **340** (entry 5). Increasing the amount of Mn(TPFC) to 0.04 eq did not make any difference (entry 6). Changing the solvent to chlorobenzene, benzene, or chloroform also did not work (entries 7 – 9).

Table 4.2. Aziridination of 2-phenyl-2*H*-chromene (**386**).



Entry	ArI=NTs	Catalyst (eq)	Solvent	Yield[a]; reaction time[b]
1	PhI=NTs	$Cu^{II}(OTf)_2$ (0.1 eq)	MeCN	5%; 3 h.
2	**340**	$Cu^{II}(OTf)_2$ (0.1 eq)	MeCN	4%; 0.5 h.
3[c]	**340**	$Cu^{II}(OTf)_2$ (0.1 eq)	MeCN	2%; 3 h.
4	PhI=NTs	Mn^{III}(TPFC) (0.01 eq)	MeCN	–[d]
5	**340**	Mn^{III}(TPFC) (0.01 eq)	MeCN	–[d]
6	**340**	Mn^{III}(TPFC) (0.04 eq)	MeCN	–[d]
7	PhI=NTs	Mn^{III}(TPFC) (0.01 eq)	PhCl	–[d]
8	PhI=NTs	Mn^{III}(TPFC) (0.01 eq)	PhH	–[d]
9	PhI=NTs	Mn^{III}(TPFC) (0.01 eq)	$CHCl_3$	–[d]
10[e]	PhI=NTs	Mn^{III}(TPFC) (0.04 eq)	**386**	–[d]
11[e]	**340**	Mn^{III}(TPFC) (0.04 eq)	**386**	–[d]
12	PhI=NTs	Cu^{I}Cl(NHC) **388** (0.1 eq)	PhCl	–[d]
13	PhI=NTs	Cu^{I}Cl(NHC) **388** (0.1 eq)	MeCN	–[d]
14	PhI=NTs	$(pyr)_4Cu^{II}(OTf)_2$ (0.1 eq)	MeCN	1%; 5 h.
15[e]	PhI=NTs	Mn^{II}(TPP)Cl (0.04 eq)	**386**	–[d]

[a] Isolated yield after chromatography. [b] Time taken for ArI=NTs to complete dissolve. [c] Run at –20 °C. [d] No aziridine was detected; $TsNH_2$ was formed. [e] Excess chromene **386** was used as solvent; 1 eq of ArI=NTs was used.

Using chromene **386** as solvent in the presence of 0.04 eq of Mn(TPFC) did not work with both PhI=NTs (entry 10) and ArI=NTs **340** (entry 11).

$Cu^{I}Cl$(NHC) catalyst **388** has been shown by Xu *et al.* to be an effective catalyst in aryliminoiodane aziridinations for both aliphatic and aromatic alkenes.[264] However, $Cu^{I}Cl$(NHC) **388** was not able to effect the aziridination of chromene **386** with PhI=NTs in chlorobenzene or acetonitrile (entries 12, 13). When $(pyr)_4Cu(OTf)_2$ was used, the reaction was complete in 5 h, but the yield obtained was very low (entry 14). Mn^{II}(TPP)Cl was also unsuccessful in effecting aziridination of chromene **386** (entry 15).

The results in Table 4.2 suggest that 2-phenyl-2*H*-chromene (**386**) is not a good substrate for aziridination, which might be due to the steric bulk of the phenyl substituent. Moreover, the hydrogen at the 2-position of the chromene **386** is also both allylic and benzylic, making **386** prone to decomposition pathways involving hydrogen atom abstraction.[276] In most cases, the *N*-tosyl aryliminoiodanes and **386** decomposed to give $TsNH_2$ and unidentified substances (black tar). However, sufficient amount of aziridine **389** was obtained in order to grow a single crystal suitable for X-ray diffraction, which confirmed the relative *trans* geometry between the aziridine ring and the phenyl substituent (Figure 4.2). Due to time constraints, we were unable to investigate the diastereoselective aziridination of other alkenes with Mn(TPFC).

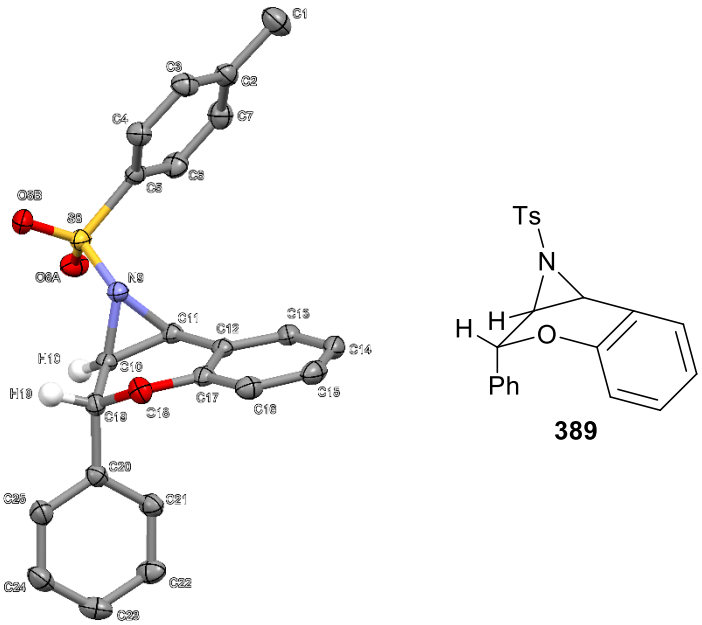


Figure 4.2. X-ray crystal structure of aziridine **389**.

4.4 Conclusions

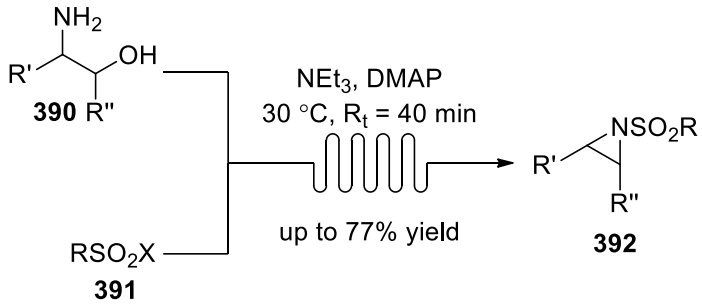
Stereocontrolled aziridinations with PhI=NTs and ArI=NTs **340** were attempted. With styrene, asymmetric reactions catalysed by copper and Evans' chiral *bis*(oxazoline) ligand **383** in MeCN showed higher enantioselectivity (29 – 30% ee) with ArI=NTs **340** compared to PhI=NTs (9 – 10%). However, upon changing to Jacobsen's chiral diimine ligand **67**, both aryliminoiodanes gave the same enantioselectivity (37 – 38% ee). This might suggest that depending on conditions, the active nitrene intermediate may or may not be bound to the iodoarene.

Attempts to use Mn(TPFC) to see if the iodoarene of the aryliminoiodane had any influence on diastereoselective aziridination of 2-phenyl-2*H*-chromene (**386**) proved unsuccessful. However, a small amount of aziridine **389** was obtained from the $Cu(OTf)_2$ catalysed aziridination of 2-phenyl-2*H*-chromene with PhI=NTs, from which a single crystal was grown. X-ray diffraction of **389** showed that the phenyl substituent was *trans* to the aziridine ring.

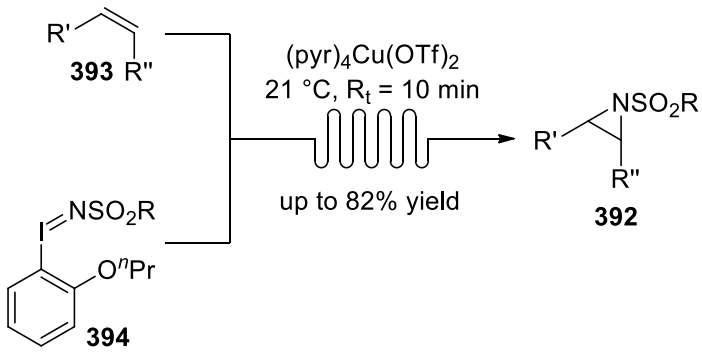
Chapter 5: Key Findings and Future Work

5.1 Key findings

This chapter gives a summary of the key findings from Chapters 2 – 4. Using continuous flow methodology, aziridine **392** can be synthesized in moderate to good yield from 1,2-amino alcohol **390** and a suitable sulfonylating agent **391** (Scheme 5.1). Alternatively, aziridination of alkene **393** with soluble *o*-propoxyaryliminoiodane **394** under continuous flow can also give similar aziridine **392** (Scheme 5.2). Both these methods have their own unique advantages. The synthesis of aziridines from 1,2-amino alcohols allows chiral aziridines to be synthesized if the 1,2-amino alcohol itself is chiral; the aziridination of alkenes has a shorter residence time with higher yields, and the starting alkenes are more readily available.

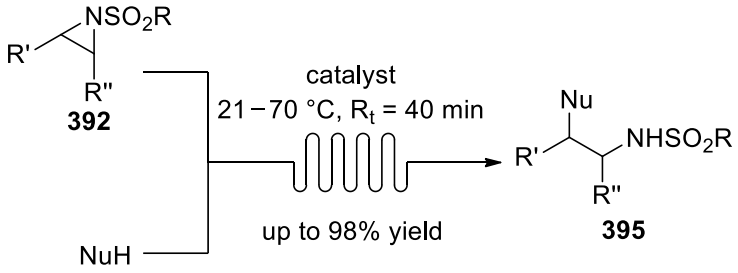


Scheme 5.1. Continuous flow synthesis of aziridines from 1,2-amino alcohols.



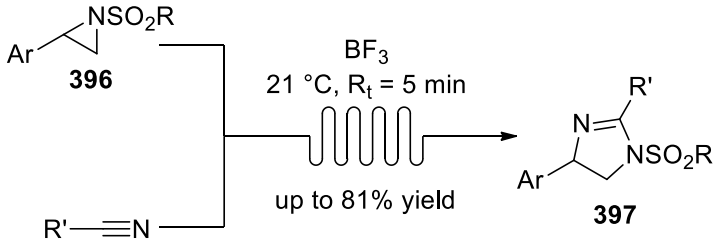
Scheme 5.2 Continuous flow synthesis of aziridines from alkenes.

The ring opening reactions of aziridines using continuous flow methodology was also explored. Various nucleophiles such as alcohols, halides, and arenes can be used to ring open aziridine **392** with excellent regioselectivity and good yields (Scheme 5.3).



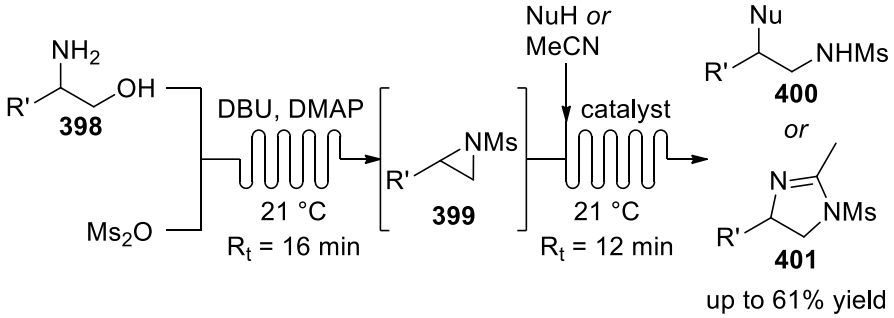
Scheme 5.3. Continuous flow ring opening of aziridines.

2-Aryl aziridine **396** can also undergo BF_3 catalysed formal [3+2] cycloadditions with nitriles to give the imidazoline **397** under continuous flow conditions (Scheme 5.4). This method gives moderate to high yields with complete regioselectivity.



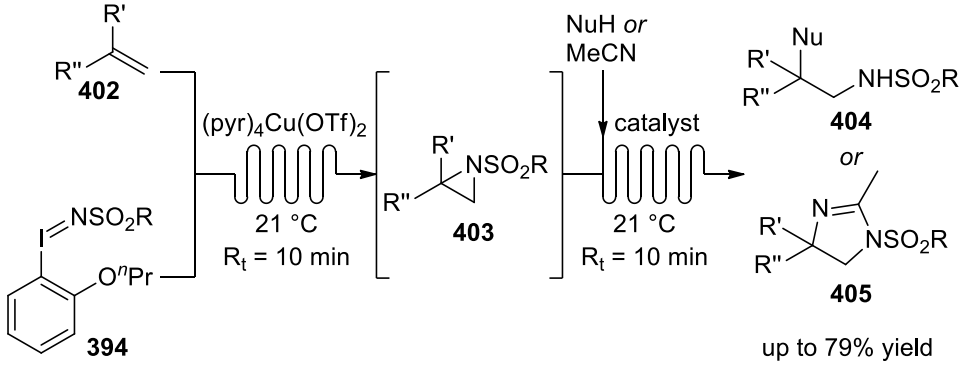
Scheme 5.4. Continuous flow [3+2] cycloadditions with 2-arylaziridines.

The continuous flow processes in Schemes 5.1 and 5.2 could be directly coupled together with those in Schemes 5.3 or 5.4. This allows the aziridine to be directly reacted with nucleophiles without having to isolate the aziridine intermediate. Starting from 1,2-amino alcohol **398**, the aziridine intermediate **399** was directly reacted with various nucleophiles to give **400** or **401** (Scheme 5.5). Ms_2O is required to prevent competitive ring opening by chloride anion from RSO_2Cl.



Scheme 5.5. Continuous flow telescoped process from 1,2-amino alcohols.

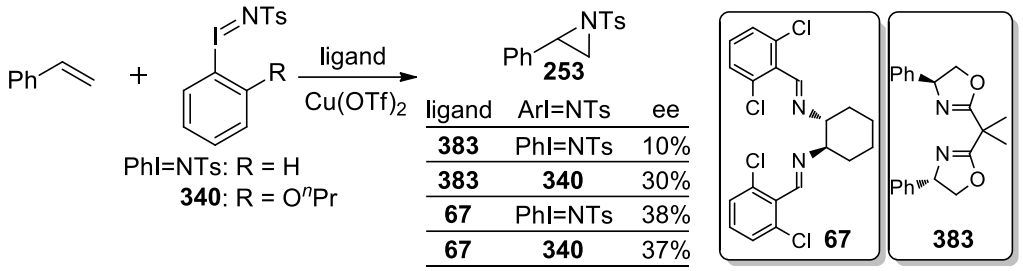
Alternatively, alkene **402** can be aziridinated by ArI=NSO_2R **394** to give *in situ* aziridine **403**, which can then be directly reacted with various nucleophiles (Scheme 5.6). This method gives higher yields and has a broader substrate scope compared to the method in Scheme 5.5. It was shown that aziridines that are difficult to isolate, such as highly reactive N-*o*Ns aziridines, can be used in this chemistry.



Scheme 5.6. Continuous flow telescoped process from alkenes.

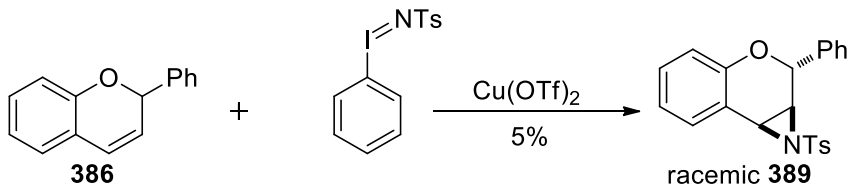
We believe that the methods outlined above provide the most general routes currently available to the generation and ring opening reactions of aziridines under continuous flow conditions.

The asymmetric aziridination of styrene with chiral ligands **67** and **383** was investigated with aryliminoiodanes PhI=NTs and **340** (Scheme 5.7). Interestingly, chiral ligand **383** gave higher enantioselectivity with ArI=NTs **340** (30% ee) compared with PhI=NTs. However, using chiral ligand **67**, the enantioselectivity for both aryliminoiodanes PhI=NTs and **340** was very similar (37 – 38% ee). This suggests that depending on the chiral ligand, the aryl group may still be associated with the active nitrene intermediate.



Scheme 5.7. Asymmetric aziridination of styrene under different conditions.

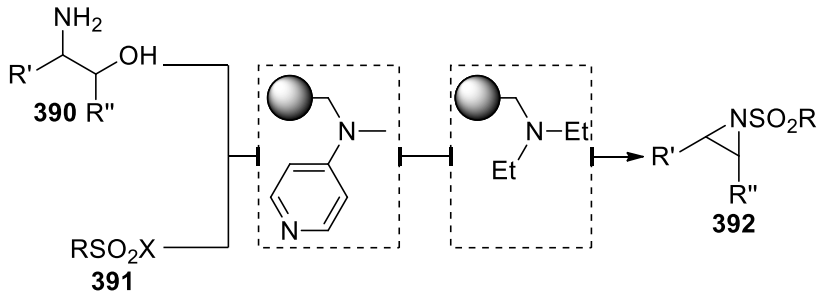
We also attempted the diastereoselective aziridination of 2-phenyl-2*H*-chromene (**386**) with different aryliminoiodanes PhI=NTs and **340**. Unfortunately, this was unsuccessful, and we only managed to obtain a small amount of aziridine **389** using PhI=NTs and $Cu(OTf)_2$ (Scheme 5.8). Diastereoselectivity could not be accurately determined due to the low yield, as well as large amounts of $TsNH_2$ and unidentified compounds produced in the reaction mixture.



Scheme 5.8. Aziridination of 2-phenyl-2*H*-chromene.

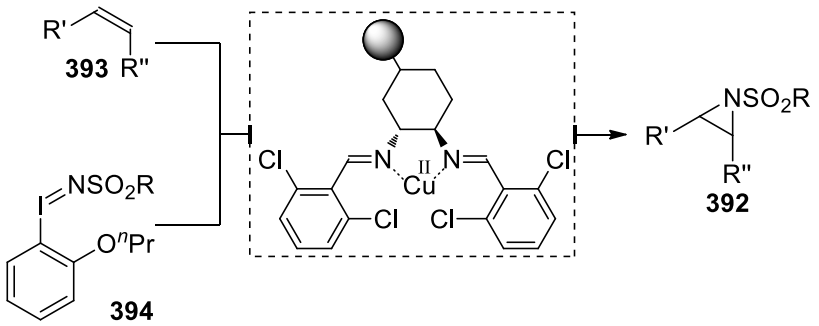
5.2 Future work

The synthesis of aziridines from 1,2-amino alcohols under continuous flow conditions could be further improved by moving to supported reagents. For example, 1,2-amino alcohol **390** and sulfonylating agent **391** could be flowed through polymer supported DMAP and NEt_3 to give aziridine **392** with less need for purification[219] (Scheme 5.9). The process described in Scheme 5.9 could be directly linked to a further ring opening step. This would have a benefit over the process in Scheme 5.5 as less acid is needed in the ring opening step as there would be no free NEt_3 in solution.



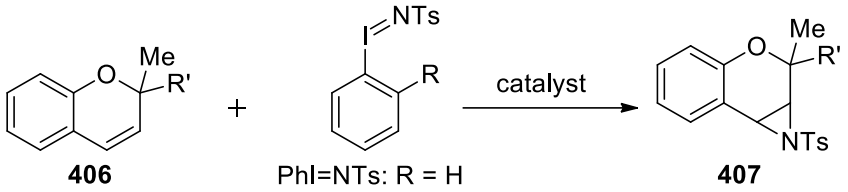
Scheme 5.9. Future work involving polymer supported DMAP and NEt_3.

Supported reagents can also be applied to the aziridination of alkenes. The use of supported copper catalysts would be an obvious extension.[277] For example, if chiral ligand **67** could be immobilized, it would be capable of chelating $Cu(OTf)_2$ catalyst, and would enable asymmetric aziridinations in flow (Scheme 5.10).



Scheme 5.10. Future work with polymer supported copper catalysts.

Investigation into the diastereoselective aziridinations of other chromenes **406** could be carried out, in which the allylic and benzylic H has been replaced with a methyl group (Scheme 5.11). This should hopefully improve the yield of aziridine **407** formed, and enable us to probe the impact of iodoarene structure on stereoselectivity.



406 PhI=NTs: R = H **340**: R = O^{n}Pr **407**

Scheme 5.11. Future work into diastereoselective aziridinations.

Chapter 6:

Experimental

6.1 General Information.

All batch reactions were performed under an atmosphere of dry nitrogen in oven dried glassware unless otherwise stated. Anhydrous solvents were purchased from Sigma-Aldrich in Sure/Seal™ bottles. All other solvents used were reagent grade and used as received. Commercially available starting materials were used without further purification unless otherwise stated. Column chromatography was carried out using Sigma-Aldrich 60 Å pore size, 40 – 64 μm particle size silica gel.

Melting points were recorded on a Gallenkamp MPD350 apparatus. Infrared spectra were recorded on a Bruker Alpha Platinum ATR spectrometer. Low resolution mass spectra were recorded on an Agilent 6130B platform with electrospray ionization. High resolution mass spectra were obtained on a Bruker MicroTOF spectrometer. Optical rotations were measured on an Optical Activity AA-1000 Polarimeter. Enantiomeric excess (ee) was determined by chiral HPLC on an Agilent 1260 Infinity system. Single crystal X-ray diffraction data were obtained by Dr Guy Clarkson on an Oxford Diffraction Gemini XRD system.

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Spectrospin DPX300 or HD300 (^{1}H at 300 MHz and ^{13}C at 75 MHz); Bruker Spectrospin DPX400 or HD400 (^{1}H at 400 MHz and ^{13}C at 100 MHz); or a Bruker Spectrospin HD500 (^{1}H at 500 MHz and ^{13}C at 125 MHz). Chemical shifts are reported in ppm using TMS as internal standard. Structures were assigned using COSY, HMQC and HMBC experiments. Peak multiplicities were recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), and coupling constants (*J*) are reported in Hertz.

6.2 Experimental set-up of flow reactors used in 6.3 – 6.10.

A custom flow system was assembled by connecting computer controlled Tricontinent C3000 syringe pumps[278] to borosilicate glass microreactor modules purchased from Little Things Factory.[279] Two different set-ups were used depending on whether the two-input or three-input configuration was required. The two-input microreactor was assembled from LTF-MX and LTF-V modules (total reaction volume = 2.0 cm^3). The three-input reactor was a XXL-S-01 module (1.0 cm^3 for first stage; 2.0 cm^3 for second stage inclusive of extra tubing). For reactions performed above room temperature, the microreactor assembly was maintained at a constant temperature by immersion in a silicone oil bath heated on a hot plate stirrer (two-input configuration), or heated directly on the hotplate (three-input configuration).

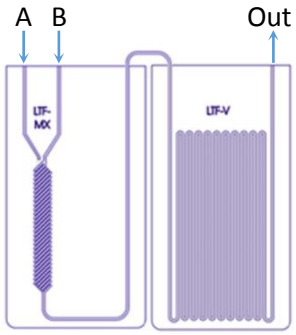


Figure 6.1: Two input microreactor setup.

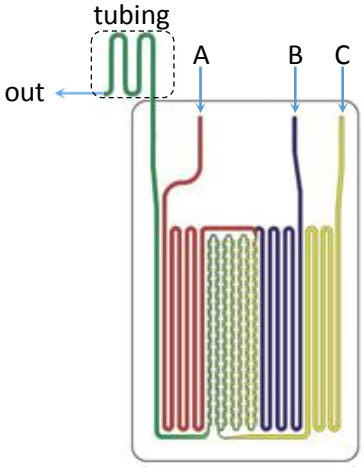
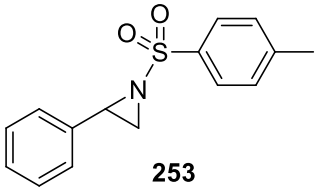


Figure 6.2: Three input microreactor setup.

6.3 General method for the flow synthesis of aziridines from 1,2-amino alcohols.

The 1,2-amino alcohol (0.50 mmol, 1 eq), base (NEt_3 for reactions involving RSO_2Cl; DBU for reactions involving Ms_2O; 2.25 mmol, 4.5 eq) and DMAP (0.25 mmol, 0.5 eq) were dissolved in $CHCl_3$ (2.0 cm^3) to produce solution A. RSO_2Cl (1.25 mmol, 2.5 eq) was dissolved in $CHCl_3$ (2.0 cm^3), or Ms_2O (1.25 mmol, 2.5 eq) in $CHCl_3/CH_2Cl_2$ (1:1, 2.0 cm^3), to give solution B. Solutions A and B were combined in the two-input microreactor (Figure 6.1.) maintained at 30°C using a 40 min residence time.

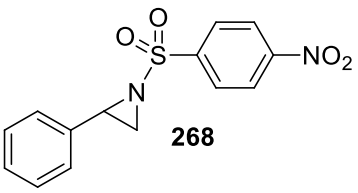
The outlet stream was quenched into a stirred solution of saturated aq NH_4Cl for reactions involving RSO_2Cl, or cooled with liquid nitrogen for reactions involving Ms_2O. Upon completion of the run, additional quantities of $CHCl_3$ were passed through the microreactor to ensure all the product was collected. For reactions involving RSO_2Cl, the crude mixture was first extracted with CH_2Cl_2 (5 × 5 cm^3), dried over $MgSO_4$ and concentrated *in vacuo*. For reactions involving Ms_2O, the frozen mixture was allowed to warm to room temperature and then concentrated *in vacuo*. The crude mixture was then purified by column chromatography (3:1; ^{n}hexane:EtOAc) to give:



253

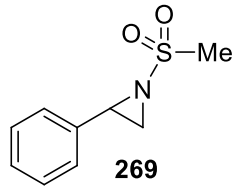
2-Phenyl-1-tosylaziridine, 253. Using 2-amino-2-phenylethan-1-ol (69 mg, 0.50 mmol), Et_3N (228 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) and TsCl (238 mg, 1.25 mmol), **253** (100 mg, 73%) was produced as a clear oil. IR (film): 1596 (C=C), 1323 (S=O), 1160 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.87 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.33 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.32 – 7.27 (3H, m, Ar*H*), 7.24 – 7.20 (2H, m,

Ar*H*), 3.78 (1H, dd, *J* = 4.5, 7.2 Hz, PhC*H*), 2.99 (1H, d, *J* = 7.2 Hz, CH*H*), 2.43 (3H, s, ArCH_3), 2.39 (1H, d, *J* = 4.5 Hz, C*H*H); δ_C (125 MHz, $CDCl_3$): 144.7 (C), 135.1 (C), 135.0 (C), 129.8 (CH), 128.6 (CH), 128.3 (CH), 128.0 (CH), 126.6 (CH), 41.1 (CH), 36.0 (CH_2), 21.7 (CH_3); *m/z* (ES^+) 296 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{15}NNaO_2S$ $[MNa]^+$: 296.0716, found: 296.0726. Using (*S*)-2-amino-2-phenylethan-1-ol, (*S*)-**253** is produced in >99% ee (Daicel Chiralcel OJ, hexane:^{i}PrOH 7:3, 0.70 cm^3/min, 254 nm, 30°C), $[\alpha]_D^{27}$ +115.6 (*c* 0.106, $CHCl_3$); literature value of $[\alpha]_D^{25}$ −108.6 (*c* 0.950, $CHCl_3$) for the (*R*) enantiomer.[239] Data consistent with that reported in literature.[19]



268

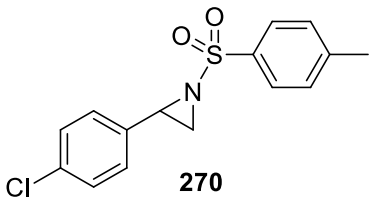
1-[(4-Nitrophenyl)sulfonyl]-2-phenyl aziridine, 268. Using 2-amino-2-phenylethan-1-ol (69 mg, 0.50 mmol), Et_3N (228 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) and ^{p}NsCl (277 mg, 1.25 mmol), **268** (90 mg, 59%) was produced as a clear oil. IR (film): 1521 (C=C), 1350 (S=O), 1158 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 8.32 (2H, d, *J* = 8.9 Hz, Ar*H*), 8.13 (2H, d, *J* = 8.9 Hz, Ar*H*), 7.28 – 7.11 (5H, m, Ar*H*), 3.84 (1H, dd, *J* = 4.6, 7.2 Hz, PhC*H*), 3.05 (1H, d, *J* = 7.2 Hz, CH*H*), 2.45 (1H, d, *J* = 4.6 Hz, CH*H*); δ_C (75 MHz, $CDCl_3$): 150.1 (C), 143.3 (C), 133.5 (C), 128.6 (CH), 128.2 (CH), 128.2 (CH), 125.9 (CH), 123.8 (CH), 41.3 (CH), 36.0 (CH_2); *m/z* (ES^+) 327 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{14}H_{12}N_2NaO_4S^+$ $[MNa]^+$: 327.0410, found: 327.0410. Data consistent with that reported in literature.[19]



269

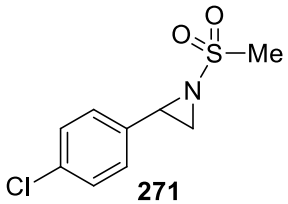
1-Mesyl-2-phenylaziridine, 269. Using 2-amino-2-phenylethan-1-ol (69 mg, 0.50 mmol), DBU (343 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) and Ms_2O (218 mg, 1.25 mmol), **269** (73 mg, 74%) was produced as a clear oil. IR (film): 1463 (C=C), 1302

(S=O), 1140 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.40 – 7.27 (5H, m, Ar*H*), 3.72 (1H, dd, *J* = 4.4, 7.3 Hz, PhC*H*), 3.10 (3H, s, CH_3), 2.98 (1H, d, *J* = 7.3 Hz, CH*H*), 2.44 (1H, d, *J* = 4.4 Hz, CH*H*); δ_C (75 MHz, $CDCl_3$): 134.9 (C), 128.8 (CH), 128.6 (CH), 126.5 (CH), 40.8 (CH), 39.8 (CH_3), 35.5 (CH_2); *m/z* (ES^+) 220 $[MNa]^+$; HRMS (ES^+) calcd. for $C_9H_{11}NNaO_2S$ $[MNa]^+$: 220.0403, found: 220.0400. Data consistent with that reported in literature.[33]



270

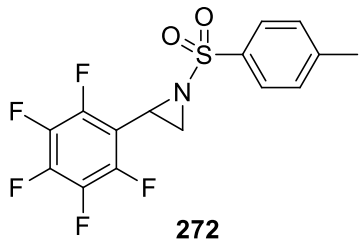
2-(4-Chlorophenyl)-1-tosylaziridine, 270. Using 2-amino-2-(4-chlorophenyl) ethan-1-ol (86 mg, 0.50 mmol), Et_3N (228 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) and TsCl (238 mg, 1.25 mmol), **270** (112 mg, 73%) was produced as a clear oil. IR (film): 1594 (C=C), 1321 (S=O), 1158 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.88 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.35 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.28 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.17 (2H, d, *J* = 8.4 Hz, Ar*H*), 3.75 (1H, dd, *J* = 4.4, 7.2 Hz, ArC*H*), 3.00 (1H, d, *J* = 7.2 Hz, C*H*H), 2.45 (3H, s, ArCH_3), 2.36 (1H, d, *J* = 4.4 Hz, C*H*H); δ_C (75 MHz, $CDCl_3$): 144.8 (C), 134.8 (C), 134.2 (C), 133.7 (C), 129.8 (CH), 128.8 (CH), 128.0 (CH), 127.9 (CH), 40.3 (CH), 36.1 (CH_2), 21.7 (CH_3); *m/z* (ES^+) 330 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{14}ClNNaO_2S$ $[MNa]^+$: 330.0326, found: 330.0322. Data consistent with that reported in literature.[28]



271

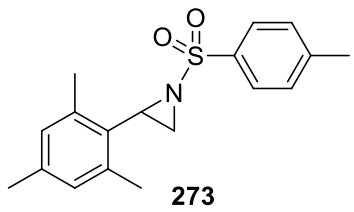
2-(4-Chlorophenyl)-1-mesylaziridine, 271. Using 2-amino-2-(4-chlorophenyl) ethan-1-ol (86 mg, 0.50 mmol), DBU (343 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) and Ms_2O (218 mg, 1.25 mmol), **271** (82 mg, 71%) was produced as a clear oil. IR (film): 1495 (C=C), 1149 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.32 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.23 (2H, d, *J* = 8.5 Hz, Ar*H*), 3.68 (1H, dd, *J* =

4.4, 7.2 Hz, ArC*H*), 3.09 (3H, s, CH_3), 2.95 (1H, d, *J* = 7.2 Hz, CH*H*), 2.38 (1H, d, *J* = 4.4 Hz, CH*H*); δ_C (75 MHz, $CDCl_3$): 134.5 (CCl), 133.5 (C), 129.0 (CH), 127.9 (CH), 39.9 (CH or CH_3), 39.8 (CH or CH_3), 35.7 (CH_2); *m/z* (ES^+) 254 $[MNa]^+$; HRMS (ES^+) calcd. for $C_9H_{10}ClNNaO_2S$ $[MNa]^+$: 254.0013, found: 254.0013.



272

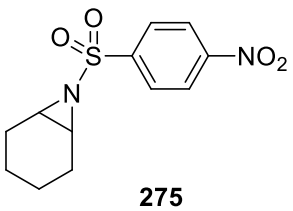
2-(Pentafluorophenyl)-1-tosylaziridine, 272. Using 2-amino-2-(pentafluorophenyl) ethan-1-ol (114 mg, 0.50 mmol), Et_3N (228 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) and TsCl (238 mg, 1.25 mmol), **272** (140 mg, 77%) was produced as a clear oil. IR (film): 1501 (C=C), 1331 (S=O), 1162 (S=O) cm^{-1}; δ_H (500 MHz, CD_2Cl_2): 7.85 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.36 (2H, d, *J* = 8.3 Hz, Ar*H*), 3.79 (1H, dd, *J* = 4.5, 7.2 Hz, ArC*H*), 3.04 (1H, d, *J* = 7.2 Hz, CH*H*), 2.80 (1H, d, *J* = 4.5 Hz, C*H*H), 2.46 (3H, s, ArCH_3); δ_C (75 MHz, $CDCl_3$): 146.1 (d, *J* = 247.7 Hz, CF), 145.3 (C), 141.3 (d, *J* = 250.7 Hz, CF), 137.6 (d, *J* = 252.9 Hz, CF), 134.1 (C), 129.9 (CH), 128.3 (CH), 108.9 (C), 32.5 (CH_2), 31.9 (CH), 21.7 (CH_3); *m/z* (ES^+) 386 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{10}F_5NNaO_2S$ $[MNa]^+$: 386.0245, found: 386.0246. Data consistent with that reported in literature.[28]



273

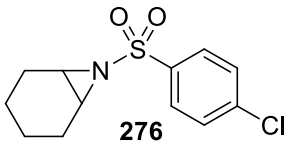
2-Mesityl-1-tosylaziridine, 273. Using 2-amino-2-mesitylethan-1-ol (90 mg, 0.50 mmol), Et_3N (228 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) and TsCl (238 mg, 1.25 mmol), **273** (62 mg, 39%) was produced as a clear oil. IR (film): 1598 (C=C), 1327 (S=O), 1156 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.87 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.34 (2H, d, *J* = 8.3 Hz, Ar*H*), 6.78 (2H, s, Ar*H*), 3.85 (1H, dd, *J* = 4.7, 7.2 Hz, ArC*H*), 2.92 (1H, d, *J* = 7.2 Hz, C*H*H), 2.44 (3H, s, ArCH_3), 2.30 (6H, s, ArCH_3), 2.22 (3H, s, ArCH_3), 2.15 (1H, d, *J* = 4.7 Hz, C*H*H); δ_C (75

MHz, $CDCl_3$): 144.7 (C), 137.5 (C), 137.4 (C), 135.1 (C), 129.7 (CH), 129.2 (CH), 128.4 (C), 128.3 (CH), 39.5 (CH), 35.5 (CH_2), 21.7 (CH_3), 20.8 (CH_3), 20.1 (CH_3); *m/z* (ES^+) 338 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{18}H_{21}NNaO_2S$ $[MNa]^+$: 338.1185, found: 338.1181. Data consistent with that reported in literature.[28]



275

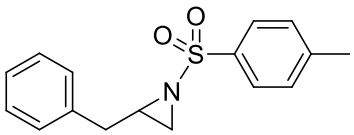
7 – [(4 – Nitrophenyl)sulfonyl] – 7 – azabicyclo[4.1.0] heptane, 275. Using *trans*-2-aminocyclohexan-1-ol (58 mg, 0.50 mmol), Et_3N (228 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) and ^{p}NsCl (277 mg, 1.25 mmol), **275** (96 mg, 68%) was produced as a clear oil. IR (film): 1607 (C=C), 1346 (S=O), 1167 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 8.39 (2H, d, *J* = 8.5 Hz, Ar*H*), 8.15 (2H, d, *J* = 8.5 Hz, Ar*H*), 3.17 – 3.10 (2H, m, NC*H*), 1.90 – 1.75 (4H, m, CH_2), 1.47 – 1.35 (2H, m, CH_2), 1.31 – 1.20 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$): 150.5 (C), 144.9 (C), 128.9 (CH), 124.3 (CH), 41.0 (CH), 22.7 (CH_2), 19.3 (CH_2); *m/z* (ES^+) 305 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{12}H_{14}N_2NaO_4S$ $[MNa]^+$: 305.0566, found: 305.0570. Data consistent with that reported in literature.[280]



276

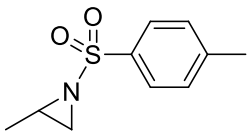
7–[(4–Chlorophenyl)sulfonyl]–7–azabicyclo[4.1.0] heptane, 276. Using *trans*-2-aminocyclohexan-1-ol (58 mg, 0.50 mmol), Et_3N (228 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) and 4-chlorobenzenesulfonyl chloride (264 mg, 1.25 mmol), **276** (41 mg, 30%) was produced as a clear oil. IR (film): 2931 (C–H), 1332 (S=O), 1158 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.89 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.52 (2H, d, *J* = 8.4 Hz, Ar*H*), 3.05 – 3.01 (2H, m, NC*H*), 1.84 – 1.76 (4H, m, CH_2), 1.49 – 1.35 (2H, m, CH_2), 1.30 – 1.17 (2H, m, CH_2); δ_C (75 MHz, $CDCl_3$): 139.1 (C), 136.9 (C), 128.7 (CH), 128.4 (CH), 39.7 (CH), 22.1 (CH_2), 18.7 (CH_2); *m/z* (ES^+) 294, 296 $[MNa]^+$; HRMS

(ES+) calcd. for $C_{12}H_{14}ClNNaO_2S$ [MNa]+: 294.0326, found: 294.0331. Data consistent with that reported in literature.[281]



277

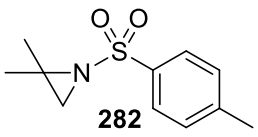
2-Benzyl-1-tosylaziridine, 277. Using 2-amino-3-phenylpropan-1-ol (76 mg, 0.50 mmol), Et_3N (228 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) and TsCl (238 mg, 1.25 mmol), **277** (60 mg, 42%) was produced as a clear oil. IR (film): 1595 (C=C), 1315 (S=O), 1156 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.60 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.13 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.10 – 6.92 (5H, m, Ar*H*), 2.91 – 2.82 (1H, m, BnC*H*), 2.73 (1H, dd, *J* = 5.1, 14.3 Hz, PhC*H*H), 2.63 (1H, d, *J* = 7.0 Hz, NC*H*H), 2.60 (1H, dd, *J* = 7.3, 14.8 Hz, PhCH*H*), 2.34 (3H, s, ArCH_3), 2.08 (1H, *J* = 4.4 Hz, NCH*H*); δ_C (75 MHz, $CDCl_3$): 143.7 (C), 136.4 (C), 134.2 (C), 129.0 (CH), 128.1 (CH), 127.8 (CH), 127.3 (CH), 125.9 (CH), 40.6 (CH), 36.9 (CH_2), 32.2 (CH_2), 21.0 (CH_3); *m/z* (ES+) 310 [MNa]+; HRMS (ES+) calcd. for $C_{16}H_{17}NNaO_2S$ [MNa]+: 310.0872, found: 310.0877. Data consistent with that reported in literature.[282]



278

2-Methyl-1-tosylaziridine, 278. Using 2-aminopropan-1-ol (38 mg, 0.51 mmol), Et_3N (228 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) and TsCl (238 mg, 1.25 mmol), **278** (55 mg, 51%) was produced as a clear oil. IR (film): 1317 (S=O), 1156 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.82 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.34 (2H, d, *J* = 8.3 Hz, Ar*H*), 2.88 – 2.77 (1H, m, C*H*Me), 2.61 (1H, d, *J* = 7.0 Hz, CH*H*), 2.44 (3H, s, ArCH_3), 2.03 (1H, d, *J* = 4.6 Hz, CH*H*), 1.25 (3H, d, *J* = 5.6 Hz, CH_3); δ_C (75 MHz, $CDCl_3$): 144.7 (C), 135.5 (C), 129.9 (CH), 128.0 (CH), 36.1 (CH), 35.0 (CH_2), 21.9 (CH_3), 17.0 (CH_3); *m/z* (ES+) 234 [MNa]+; HRMS (ES+) calcd. for $C_{10}H_{13}NNaO_2S$ [MNa]+: 234.0559, found: 234.0565. Data consistent with that reported in literature.[282]

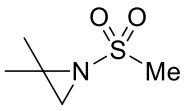
6.4 Flow synthesis of 2,2-dimethyl-1-tosylaziridine, 282.



282

2-Amino-2-methylpropan-1-ol (45 mg, 0.50 mmol, 1 eq) and DMAP (128 mg, 1.05 mmol, 2.1 eq) were dissolved in $CHCl_3$ (2.0 cm^3) to give solution A. TsCl (200 mg, 1.05 mmol, 2.1 eq) was dissolved in $CHCl_3$ (2.0 cm^3) to give solution B. DBU (343 mg, 2.25 mmol, 4.5 eq) was dissolved in $CHCl_3$ (4.0 cm^3) to give solution C. These solutions were combined in the three-input microreactor (Figure 6.2). The syringe pump additions were adjusted to give a 15 min residence time for the initial combination of solutions A and B; and a further 15 min residence time upon addition of solution C. The outlet stream was quenched into a stirred solution of saturated aq NH_4Cl. Upon completion of the run, additional quantities of $CHCl_3$ were passed through the microreactor to ensure all the product was collected. The resulting mixture was extracted with CH_2Cl_2 (5 × 5 cm^3), the combined organic extracts dried over $MgSO_4$, and solvent removed *in vacuo*. Purification by column chromatography (3:1; ^{n}hexane:EtOAc) gave **282** (41 mg, 36%) as a clear oil. IR (film): 1596 (C=C), 1302 (S=O), 1155 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.83 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.31 (2H, d, *J* = 8.3 Hz, Ar*H*), 2.44 – 2.42 (5H, m, ArCH_3 and CH_2), 1.54 (6H, s, CH_3); δ_C (125 MHz, $CDCl_3$): 143.8 (C), 138.1 (C), 129.5 (CH), 127.3 (CH), 47.9 (C), 42.0 (CH_2), 22.9 (CH_3), 21.6 (CH_3); *m/z* (ES^+) 226 $[MH]^+$; HRMS (ES^+) calcd. for $C_{11}H_{16}NO_2S$ $[MH]^+$: 226.0896, found: 226.0894.

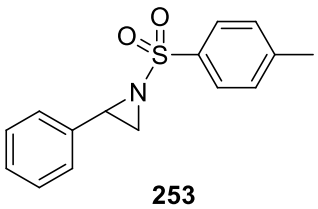
6.5 Flow synthesis of 2,2-dimethyl-1-(mesyl)aziridine, 283.



283

2-Amino-2-methylpropan-1-ol (45 mg, 0.50 mmol, 1 eq) and DMAP (128 mg, 1.05 mmol, 2.1 eq) were dissolved in $CHCl_3$ (2.0 cm^3) to give solution A. Ms_2O (183 mg, 1.05 mmol, 2.1 eq) was dissolved in $CHCl_3/CH_2Cl_2$ (1:1, 2.0 cm^3) to give solution B. DBU (343 mg, 2.25 mmol, 4.5 eq) was dissolved in $CHCl_3$ (4.0 cm^3) to give solution C. These solutions were combined in the three-input microreactor (Figure 6.2). The syringe pump additions were adjusted to give a 15 min residence time for the initial combination of solutions A and B; and a further 15 min residence time upon addition of solution C. The outlet stream was cooled with liquid N_2 to inhibit further reaction. Upon completion of the run, additional quantities of $CHCl_3$ were passed through the microreactor to ensure all the product was collected. The crude mixture was purified by column chromatography (3:1; ^{n}hexane:EtOAc) to give **283** (25 mg, 34%) as a clear oil. IR (film): 1304 (S=O), 1149 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 3.06 (3H, s, SO_2CH_3), 2.44 (2H, s, CH_2), 1.53 (6H, s, $C(CH_3)_2$); δ_C (125 MHz, $CDCl_3$): 47.0 (C), 42.2 (CH_3), 42.0 (CH_2), 22.8 (CH_3); *m/z* (ES^+) 172 $[MNa]^+$; HRMS (ES^+) calcd. for $C_5H_{11}NNaO_2S$ $[MNa]^+$: 172.0403, found: 172.0403.

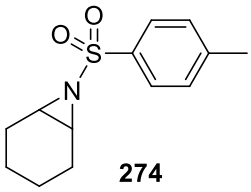
6.6 Large scale batch synthesis of 2-phenyl-1-tosylaziridine, 253.



253

NaNTsCl·3H_2O (16.5 g, 58.6 mmol, 1.2 eq) and ^{n}Bu$_4$NBr (1.59 g, 4.93 mmol, 0.1 eq) were dissolved in H_2O (75 cm^3). CH_2Cl_2 (100 cm^3) was then added, and to this mixture was added styrene (5.09 g, 48.9 mmol, 1 eq) and I_2 (1.25 g, 4.92 mmol, 0.1 eq). The mixture was stirred for 24 h at r.t. An orange-brown mixture/ emulsion was obtained immediately. After 24 h, $Na_2S_2O_3$ (2.50 g, 15.8 mmol, 0.3 eq) was added. After 15 min, the mixture was extracted with CH_2Cl_2 (4 × 100 cm^3). The combined organic layers were washed with saturated aq NaCl (200 cm^3), dried with $MgSO_4$, filtered, and the solvent removed *in vacuo* to give a yellow oil. Recrystallization from ^{n}hexane gave **253** (6.37 g, 48%) as off-white crystals. M.p. 90 – 93 °C. Other data as previously reported.[33]

6.7 Large scale batch synthesis of 7-tosyl-7-azabicyclo[4.1.0]heptane, 274.



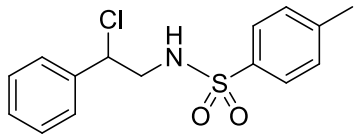
274

Cyclohexene (4.06 g, 49.4 mmol, 1 eq) was dissolved in CH_2Cl_2 (25 cm^3). To the solution was added H_2O (75 cm^3). NaNTsCl·3H_2O (16.7 g, 59.3 mmol, 1.2 eq), I_2 (1.25 g, 4.92 mmol, 0.1 eq), and ^{n}Bu$_4$NBr (1.59 g, 4.93 mmol, 0.1 eq) were added, and the mixture stirred for 24 h at r.t. A brownish-orange suspension formed immediately. After 24 h, the mixture was extracted with CH_2Cl_2 (4 × 100 cm^3). The combined organic layers were washed with saturated aq $Na_2S_2O_3$ (200 cm^3), then saturated aq NaCl (200 cm^3), dried with $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting oil was purified by column chromatography (5:1 ^{n}hexane:EtOAc), then recrystallized (^{n}hexane) to give **274** (4.48 g, 36%) as pure white crystals. M.p. 57 – 58 °C. IR (film): 2939 (C–H), 1597 (C=C), 1320 (S=O), 1156 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.82 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.33 (2H, d, *J* = 8.3 Hz, Ar*H*), 2.97

(2H, t, *J* = 1.3 Hz, NC*H*), 2.44 (3H, s, ArCH_3), 1.85 – 1.76 (4H, m, CH_2), 1.44 – 1.17 (4H, m, CH_2); δ_C (75 MHz, $CDCl_3$): 144.0 (C), 135.8 (C), 129.6 (CH), 127.6 (CH), 39.8 (CH), 22.8 (CH_2), 21.6 (CH_3), 19.4 (CH_2); *m/z* (ES^+) 274 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{13}H_{17}NNaO_2S$ $[MNa]^+$: 274.0872, found: 274.0874. Data consistent with that reported in literature.[281]

6.8 General method for the ring opening of aziridines in flow.

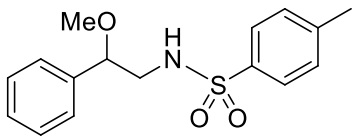
The aziridine (0.50 mmol, 1 eq) in solvent A (2.0 cm^3) was reacted with the nucleophile and catalyst dissolved in solvent B (2.0 cm^3) using the two-input microreactor (Figure 6.1) maintained at the stated temperature with a 40 min residence time. The outlet stream was quenched into saturated aq $NaHCO_3$ solution. Upon completion of the run, additional quantities of the solvents were passed through the microreactor to ensure all the product was collected. The mixture was extracted with CH_2Cl_2 (5 × 5 cm^3), the combined organic extracts dried over $MgSO_4$, and solvent removed *in vacuo*. Purification by column chromatography gave the following products:



291

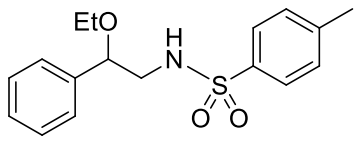
***N*-(2 –Chloro - 2- phenylethyl)-4-methylbenzene sulfonamide, 291.** Aziridine **253** (137 mg, 0.50 mmol) in $CHCl_3$ (2.0 cm^3) was combined with a solution of HCl (2M in Et_2O, 1.0 cm^3) in $CHCl_3$ (1.0 cm^3) at 70 °C as described above. After work-up and chromatography (3:1; ^{n}hexane:EtOAc), **291** (107 mg, 69%) was obtained as a clear oil. IR (film): 3256 (N–H), 1596 (C=C), 1156 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.73 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.38 – 7.26 (7H, m, Ar*H*), 4.87 (1H, dd, *J* = 6.0, 8.2 Hz, PhC*H*), 4.78 (1H, t, *J* = 6.4 Hz, N*H*), 3.53 – 3.37 (2H, m, CH_2), 2.45 (3H, s, ArCH_3); δ_C (75 MHz, $CDCl_3$): 143.3 (C), 137.2 (C), 136.3 (C), 129.3 (CH), 128.5

(CH), 128.3 (CH), 126.6 (CH), 126.4 (CH), 61.1 (CH), 49.8 (CH_2), 21.0 (CH_3); *m/z* (ES^+) 332, 334 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{16}ClNNaO_2S$ $[MNa]^+$: 332.0482, found: 332.0488. Data consistent with that reported in literature.[232]



292

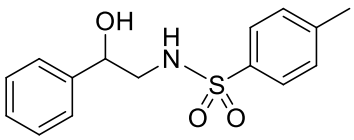
***N*-(2-Methoxy-2-phenylethyl)-4-methylbenzene sulfonamide, 292.** Aziridine **253** (137 mg, 0.50 mmol) in $CHCl_3$ (2.0 cm^3) was combined with H_2SO_4 (147 mg, 1.50 mmol) in MeOH (2.0 cm^3) at 70 °C as described above. After work-up and chromatography (3:1; ^{n}hexane:EtOAc), **292** (148 mg, 97%) was obtained as a clear oil. IR (film): 3282 (N–H), 1601 (C=C), 1159 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.73 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.35 – 7.18 (7H, m, Ar*H*), 5.15 (1H, dd, *J* = 2.9, 9.3 Hz, N*H*), 4.20 (1H, dd, *J* = 3.6, 9.3 Hz, PhC*H*), 3.26 – 3.17 (1H, m, CH*H*), 3.16 (3H, s, OCH_3), 3.01 – 2.91 (1H, m, CH*H*), 2.42 (3H, s, ArCH_3); δ_C (75 MHz, $CDCl_3$): 143.5 (C), 138.3 (C), 137.0 (C), 129.8 (CH), 128.7 (CH), 128.4 (CH), 127.1 (CH), 126.6 (CH), 82.1 (CH), 56.8 (CH_3), 49.4 (CH_2), 21.6 (CH_3); *m/z* (ES^+) 328 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{16}H_{19}NNaO_3S$ $[MNa]^+$: 328.0978, found: 328.0979. Data consistent with that reported in literature.[244]



293

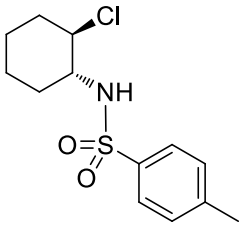
***N*-(2– Ethoxy - 2-phenylethyl)-4-methylbenzene sulfonamide, 293.** Aziridine **253** (137 mg, 0.50 mmol) in $CHCl_3$ (2.0 cm^3) was combined with H_2SO_4 (147 mg, 1.50 mmol) in EtOH (2.0 cm^3) at 70 °C as described above. After work-up and chromatography (3:1; ^{n}hexane:EtOAc), **293** (62 mg, 39%) was obtained as a clear oil. IR (film): 3284 (N–H), 1597 (C=C), 1164 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.72 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.35 – 7.18 (7H, m, Ar*H*), 4.96 (1H, dd, *J* = 2.7, 9.4 Hz, N*H*), 4.31 (1H, dd, *J* = 3.7, 9.4 Hz, PhC*H*), 3.41 – 3.19 (2H, m, OCH_2CH_3), 3.25 – 3.15

(1H, m, CH*H*), 2.98 – 2.90 (1H, m, CH*H*), 2.42 (3H, s, ArCH_3), 1.14 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); δ_C (125 MHz, $CDCl_3$): 143.5 (C), 139.0 (C), 137.0 (C), 129.7 (CH), 128.6 (CH), 128.3 (CH), 127.1 (CH), 126.5 (CH), 80.2 (CH), 64.4 (CH_2), 49.4 (CH_2), 21.5 (CH_3), 15.2 (CH_3); *m/z* (ES^+) 342 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{17}H_{21}NNaO_3S[MNa]^+$: 342.1134, found: 342.1143. Data consistent with that reported in literature.[244]



294

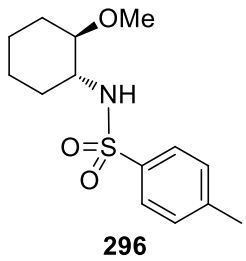
2-(Tosylamino)-1-phenylethan-1-ol, 294. Aziridine **253** (137 mg, 0.50 mmol) in acetone (2.0 cm^3) was combined with H_2SO_4 (147 mg, 1.50 mmol) and H_2O (200 mg, 11.1 mmol) in acetone (2.0 cm^3) at 70 °C as described above. After work-up and chromatography (3:1; ^{n}hexane:EtOAc), **294** (143 mg, 98%) was obtained as a clear oil. IR (film): 3398, 3147, 1598 (C=C), 1146 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.73 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.38 – 7.26 (7H, m, Ar*H*), 5.03 (1H, dd, *J* = 4.5, 7.7 Hz, N*H*), 4.85 – 4.75 (1H, m, PhC*H*), 3.32 – 3.18 (1H, m, CH*H*), 3.10 – 2.96 (1H, m, CH*H*), 2.54 (1H, d, *J* = 3.5 Hz, O*H*), 2.42 (3H, s, ArCH_3); δ_C (75 MHz, $CDCl_3$): 143.6 (C), 140.8 (C), 136.7 (C), 129.8 (CH), 128.7 (CH), 128.2 (CH), 127.1 (CH), 125.9 (CH), 72.8 (CH), 50.2 (CH_2), 21.6 (CH_3); *m/z* (ES^+) 314 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{17}NNaO_3S$ $[MNa]^+$: 314.0821, found: 314.0820. Data consistent with that reported in literature.[164]



295

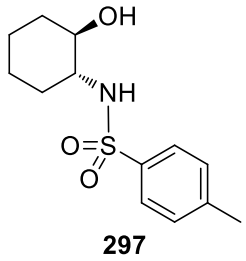
***trans*-*N*-(2-Chlorocyclohexyl)-4-methylbenzenesulfonamide, 295.** Aziridine **274** (126 mg, 0.50 mmol) in $CHCl_3$ (2.0 cm^3) was combined with a solution of HCl (2M in Et_2O, 1.0 cm^3) in $CHCl_3$ (1.0 cm^3) at 70 °C as described above. After work-up and chromatography (1:1; ^{n}hexane:EtOAc), **295** (141 mg, 98%) was

obtained as a clear oil. IR (film): 3250 (N–H), 1594 (C=C), 1152 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.78 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.30 (2H, d, *J* = 8.3 Hz, Ar*H*), 5.07 (1H, d, *J* = 5.4 Hz, N*H*), 3.71 (1H, td, *J* = 4.2, 9.6 Hz, ClC*H*), 3.18 – 3.01 (1H, m, NC*H*), 2.43 (3H, s, ArCH_3), 2.28 – 2.12 (2H, m, CH_2), 1.76 – 1.56 (3H, m, CH_2), 1.35 – 1.21 (3H, m, CH_2); δ_C (75 MHz, $CDCl_3$): 143.1 (C), 136.7 (C), 129.1 (CH), 126.9 (CH), 61.9 (CH), 58.2 (CH), 34.4 (CH_2), 31.9 (CH_2), 23.8 (CH_2), 22.8 (CH_2), 21.0 (CH_3); *m/z* (ES^+) 310, 312 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{13}H_{18}ClNNaO_2S$ $[MNa]^+$: 310.0639, found: 310.0640. Data consistent with that reported in literature.[232]



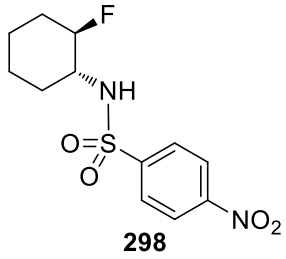
296

***trans*-*N*-(2-Methoxycyclohexyl)-4-methylbenzenesulfonamide, 296.** Aziridine **274** (126 mg, 0.50 mmol) in $CHCl_3$ (2.0 cm^3) was combined with H_2SO_4 (147 mg, 1.50 mmol) in MeOH (2.0 cm^3) at 70 °C as described above. After work-up and chromatography (3:1; ^{n}hexane:EtOAc), **296** (102 mg, 72%) was obtained as a clear oil. IR (film): 3277 (N–H), 1598 (C=C), 1155 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.78 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.30 (2H, d, *J* = 8.3 Hz, Ar*H*), 5.37 – 5.31 (1H, m, N*H*), 3.18 (3H, s, OCH_3), 2.98 – 2.81 (2H, m, NC*H* and (MeO)C*H*), 2.42 (3H, s, ArCH_3), 2.20 – 1.90 (2H, m, CH_2), 1.71 – 1.53 (2H, m, CH_2), 1.30 – 1.01 (4H, m, CH_2); δ_C (75 MHz, $CDCl_3$): 142.4 (C), 136.9 (C), 128.9 (CH), 126.6 (CH), 80.7 (CH), 56.3 (CH), 55.3 (CH_3), 30.6 (CH_2), 28.0 (CH_2), 23.0 (CH_2), 22.7 (CH_2), 20.9 (CH_3); *m/z* (ES^+) 306 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{14}H_{21}NNaO_3S$ $[MNa]^+$: 306.1134, found: 306.1143. Data consistent with that reported in literature.[244]



297

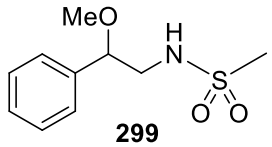
***trans-N*-(2-Hydroxycyclohexyl)-4-methylbenzenesulfon amide, 297.** Aziridine **274** (126 mg, 0.50 mmol) in acetone (2.0 cm^3) was combined with H_2SO_4 (147 mg, 1.50 mmol) and H_2O (200 mg, 11.1 mmol) in acetone (2.0 cm^3) at 70 °C as described above. After work-up and chromatography (3:1; ^{n}hexane:EtOAc), **297** (101 mg, 75%) was obtained as a clear oil. IR (film): 3541, 3259, 1597 (C=C), 1149 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.82 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.31 (2H, d, *J* = 8.3 Hz, Ar*H*), 5.62 (1H, d, *J* = 6.7 Hz, N*H*), 3.34 (1H, td, *J* = 4.2, 9.7 Hz, (HO)C*H*), 3.22 (1H, s, O*H*), 2.94 – 2.82 (1H, m, NC*H*), 2.42 (3H, s, ArCH_3), 2.05 – 1.96 (1H, m, CH_2), 1.71 – 1.50 (3H, m, CH_2), 1.30 – 1.08 (4H, m, CH_2); δ_C (75 MHz, $CDCl_3$): 143.5 (C), 137.6 (C), 129.8 (CH), 127.1 (CH), 73.1 (CH), 59.7 (CH), 33.4 (CH_2), 31.6 (CH_2), 24.7 (CH_2), 23.9 (CH_2), 21.6 (CH_3); *m/z* (ES^+) 292 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{13}H_{19}NNaO_3S$ $[MNa]^+$: 292.0978, found: 292.0980. Data consistent with that reported in literature.[244]



298

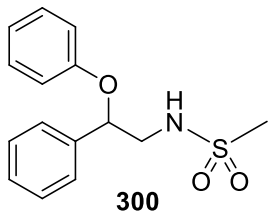
***trans* - *N* -(2-Fluorocyclohexyl)-4-nitrobenzenesulfon amide, 298.** Aziridine **275** (142 mg, 0.50 mmol) in $CHCl_3$ (2.0 cm^3) was combined with $BF_3{\cdot}OEt_2$ (213 mg, 1.50 mmol) and ^{i}PrOH (90 mg, 1.50 mmol) in $CHCl_3$ (2.0 cm^3) at 21 °C as described above. After work-up and chromatography (3:1; ^{n}hexane:EtOAc), **298** (95 mg, 63%) was obtained as a crystalline solid. M.p. 174 – 175 °C. IR (film): 3345 (N–H), 1603 (C=C), 1163 (S=O) cm^{-1}; δ_H (500 MHz, CD_2Cl_2): 8.32 (2H, d, *J* = 8.9 Hz, Ar*H*), 8.05 (2H, d, *J* = 8.9 Hz, Ar*H*), 4.92 (1H, d, *J* = 6.8 Hz, N*H*), 4.22 – 4.04 (1H, dm, *J* = 50.2 Hz, FC*H*), 3.31 – 3.22 (1H, m, NC*H*), 2.09 – 1.99 (2H, m, CH_2), 1.75 – 1.59 (2H, m, CH_2), 1.45 – 1.34 (1H, m, CH_2), 1.30 – 1.15 (3H, m, CH_2); δ_C (125 MHz, CD_2Cl_2): 150.1 (C), 146.8 (C), 128.4 (CH), 124.3 (CH), 93.6 (d, *J* = 179.2

Hz, CH), 57.5 (d, *J* = 17.5 Hz, CH), 32.2 (CH_2), 31.2 (CH_2), 23.9 (CH_2), 23.0 (CH_2); *m/z* (ES^+) 325 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{12}H_{15}N_2FNaO_4S$ $[MNa]^+$: 325.0629, found: 325.0626.



299

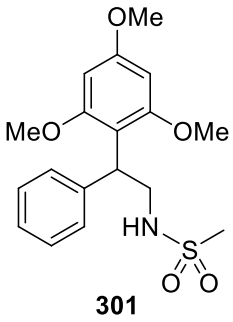
***N*-(2 – Methoxy - 2-phenylethyl)methanesulfonamide, 299.** Aziridine **269** (99 mg, 0.50 mmol) in $CHCl_3$ (2.0 cm^3) was combined with H_2SO_4 (147 mg, 1.50 mmol) in MeOH (2.0 cm^3) at 70 °C as described above. After work-up and chromatography (1:1; ^{n}hexane:EtOAc), **299** (84 mg, 73%) was obtained as a clear oil. IR (film): 3278 (N–H), 1453 (C=C), 1147 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.42 – 7.29 (5H, m, Ar*H*), 4.92 – 4.87 (1H, m, N*H*), 4.34 (1H, dd, *J* = 3.7, 8.5 Hz, PhC*H*), 3.39 – 3.32 (1H, m, CH*H*), 3.28 (3H, s, OCH_3), 3.26 – 3.20 (1H, m, CH*H*), 2.90 (3H, s, SO_2CH_3); δ_C (125 MHz, $CDCl_3$): 138.3 (C), 128.8 (CH), 128.5 (CH), 126.7 (CH), 82.5 (CH), 56.9 (CH_3), 49.4 (CH_2), 40.4 (CH_3); *m/z* (ES^+) 252 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{10}H_{15}NNaO_3S$ $[MNa]^+$: 252.0665, found: 252.0661.



300

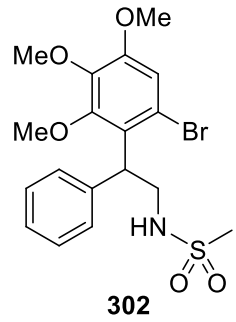
***N*-(2 – Phenoxy - 2-phenylethyl)methanesulfonamide, 300.** Aziridine **269** (99 mg, 0.50 mmol) in $CHCl_3$ (2.0 cm^3) was combined with PhOH (235 mg, 2.50 mmol) and MsOH (240 mg, 2.50 mmol) in $CHCl_3$ (2.0 cm^3) at 21 °C as described above. After work-up and chromatography (1:1; ^{n}hexane:EtOAc), **300** (77 mg, 53%) was obtained as a clear oil. IR (film): 3286 (N–H), 1596 (C=C), 1144 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.29 – 7.15 (5H, m, Ar*H*), 7.11 – 7.03 (2H, m, Ar*H*), 6.81 – 6.68 (3H, m, Ar*H*), 5.24 – 5.14 (1H, m, PhC*H*), 4.84 (1H, dd, *J* = 5.0, 7.4 Hz, N*H*), 3.50 – 3.30 (2H, m, CH_2), 2.76 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$): 156.6 (C), 137.3 (C), 128.9 (CH), 128.3 (CH), 127.9 (CH), 125.6 (CH), 120.9 (CH), 115.2 (CH), 78.4

(CH), 49.0 (CH_2), 40.2 (CH_3); *m/z* (ES^+) 314 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{17}NNaO_3S$ $[MNa]^+$: 314.0821, found: 314.0828.



301

***N*–[2–Phenyl–2–(2,4,6–trimethoxyphenyl)ethyl]methane sulfonamide, 301.** Aziridine **269** (99 mg, 0.50 mmol) in $CHCl_3$ (2.0 cm^3) was combined with 1,3,5-trimethoxybenzene (420 mg, 2.50 mmol) and MsOH (240 mg, 2.50 mmol) in $CHCl_3$ (2.0 cm^3) at 21 °C as described above. After work-up and chromatography (1:1; ^{n}hexane:EtOAc), **301** (93 mg, 51%) was obtained as a crystalline solid. M.p. 158 – 159 °C. IR (film): 3313 (N–H), 1587 (C=C), 1145 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.28 – 7.22 (4H, m, Ar*H*), 7.18 – 7.13 (1H, m, Ar*H*), 6.13 (2H, s, Ar*H*), 4.80 (1H, dd, *J* = 6.9, 9.4 Hz, PhC*H*), 4.32 – 4.25 (1H, m, N*H*), 3.98 – 3.85 (2H, m, CH_2), 3.80 (3H, s, OCH_3), 3.74 (6H, s, OCH_3), 2.78 (3H, s, SO_2CH_3); δ_C (125 MHz, $CDCl_3$): 160.5 (C), 159.4 (C), 141.9 (C), 128.1 (CH), 127.8 (CH), 126.2 (CH), 109.3 (C), 91.3 (CH), 55.7 (CH_3), 55.3 (CH_3), 45.6 (CH_2), 40.3 (CH or CH_3), 40.2 (CH or CH_3); *m/z* (ES^+) 388 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{18}H_{23}NNaO_5S$ $[MNa]^+$: 388.1189, found: 388.1190.



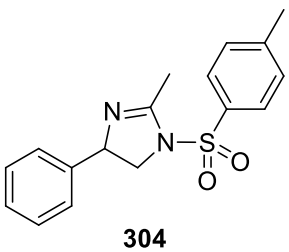
302

***N*-[2 - (6-Bromo-2,3,4-trimethoxyphenyl)-2-phenylethyl] methanesulfonamide, 302.** Aziridine **269** (99 mg, 0.50 mmol) in $CHCl_3$ (2.0 cm^3) was combined with 5-bromo-1,2,3-trimethoxybenzene (618 mg, 2.50 mmol) and MsOH (240 mg, 2.50 mmol) in $CHCl_3$ (2.0 cm^3) at 21 °C as described above. After work-up and chromatography (1:1; ^{n}hexane:EtOAc), **302** (31 mg, 14%) was obtained as an oil. IR (film): 3277 (N–H), 1585 (C=C), 1117 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.33 – 7.18 (5H, m, Ar*H*), 6.94 (1H, s, Ar*H*), 4.84 (1H, t, *J* = 7.5 Hz,

PhC*H*), 4.50 – 4.40 (1H, m, N*H*), 4.03 – 3.97 (2H, m, CH_2), 3.86 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 2.82 (3H, s, SO_2CH_3); δ_C (125 MHz, $CDCl_3$): 153.4 (C), 153.2 (C), 142.4 (C), 140.8 (C), 128.4 (CH), 127.3 (CH), 127.1 (C), 126.6 (CH), 119.3 (C), 111.9 (CH), 60.6 (CH_3), 60.4 (CH_3), 56.2 (CH_3), 47.7 (CH), 44.7 (CH_2), 40.3 (CH_3); *m/z* (ES^+) 466 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{18}H_{22}BrNNaO_5S$ $[MNa]^+$: 466.0294, found: 466.0294.

6.9 General flow procedure for ring expansion of aziridines to imidazolines.

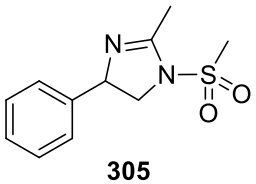
The aziridine (0.50 mmol, 1 eq) was dissolved in CH_2Cl_2 (2.0 cm^3) to give solution A. $Et_2O{\cdot}BF_3$ (2.50 mmol, 5.0 eq) and the appropriate nitrile (2.50 mmol, 5.0 eq) were dissolved in CH_2Cl_2 (2.0 cm^3) to give solution B. These two solutions were combined in the two-input microreactor (Figure 6.1) at 21°C using a 5 min residence time. The outlet stream was quenched into saturated aq $NaHCO_3$. Upon completion of the run, additional quantities of CH_2Cl_2 were passed through the microreactor to ensure all the product was collected. The resulting mixture was extracted with CH_2Cl_2 (5 × 5 cm^3), the combined organic extracts dried over $MgSO_4$, and solvent removed *in vacuo*. Purification by column chromatography (EtOAc) gave the following products:



304

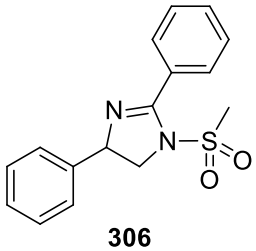
2-Methyl-4-phenyl-1-(4-methylbenzenesulfonyl)-4,5-dihydro-1*H*-imidazole, 304. Using aziridine **253** (137 mg, 0.50 mmol), $BF_3{\cdot}OEt_2$ (309 µL, 2.50 mmol), MeCN (131 µL, 2.51 mmol), imidazoline **304** (115 mg, 73%) was produced as a clear oil. IR (film): 1645, 1356 (S=O), 1165 (S=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.77 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.36 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.32 – 7.24 (3H, m, Ar*H*), 7.10 – 7.03 (2H, m, Ar*H*), 5.04 – 4.97 (1H, m, PhC*H*), 4.19 (1H, t, *J* = 10.0

Hz, CH*H*), 3.64 (1H, dd, *J* = 8.0, 10.0 Hz, CH*H*), 2.47 (3H, s, ArCH_3), 2.43 – 2.41 (3H, m, CH_3); δ_C (75 MHz, $CDCl_3$): 156.3 (C), 144.8 (C), 141.6 (C), 135.2 (C), 130.2 (CH), 128.7 (CH), 127.7 (CH), 127.3 (CH), 126.4 (CH), 66.7 (CH), 55.5 (CH_2), 21.6 (CH_3), 16.9 (CH_3); *m/z* (ES^+) 315 $[MH]^+$; HRMS (ES^+) calcd. for $C_{17}H_{19}N_2O_2S$ $[MH]^+$: 315.1162, found: 315.1162. Data consistent with that reported in literature.[283]



305

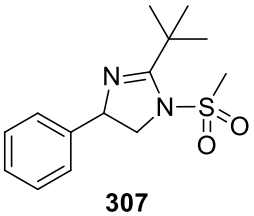
2-Methyl-1-methylsulfonyl-4-phenyl-4,5-dihydro-1*H*-imidazole, 305. Using aziridine **269** (99 mg, 0.50 mmol), $BF_3{\cdot}OEt_2$ (309 μL, 2.50 mmol), MeCN (131 μL, 2.51 mmol), imidazoline **305** (85 mg, 71%) was produced as a crystalline solid. M.p. 97 – 100 °C. IR (film): 1646, 1348 (S=O), 1161 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.39 – 7.24 (5H, m, Ar*H*), 5.16 – 5.10 (1H, m, PhC*H*), 4.25 (1H, t, *J* = 9.8 Hz, CH*H*), 3.70 (1H, dd, *J* = 8.2, 9.8 Hz, CH*H*), 3.04 (3H, s, SO_2CH_3), 2.39 – 2.34 (3H, m, CH_3); δ_C (125 MHz, $CDCl_3$): 156.0 (C), 141.5 (C), 128.9 (CH), 127.9 (CH), 126.4 (CH), 66.7 (CH), 55.7 (CH_2), 39.2 (CH_3), 16.7 (CH_3); *m/z* (ES^+) 239 $[MH]^+$; HRMS (ES^+) calcd. for $C_{11}H_{15}N_2O_2S$ $[MH]^+$: 239.0849, found: 239.0854.



306

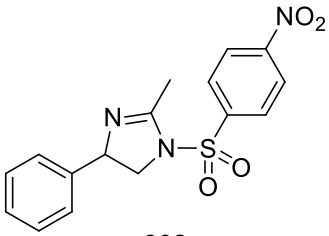
1 – (Methylsulfonyl) –2, 4 – diphenyl – 4, 5 –dihydro–1*H*-imidazole, 306. Using aziridine **269** (99 mg, 0.50 mmol), $BF_3{\cdot}OEt_2$ (309 μL, 2.50 mmol), PhCN (258 mg, 2.50 mmol), imidazoline **306** (87 mg, 58%) was produced as a crystalline solid. M.p. 131 – 132 °C. IR (film): 1621, 1346 (S=O), 1155 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.79 (2H, d, *J* = 7.3 Hz, Ar*H*), 7.51 (1H, t, *J* = 7.3 Hz, Ar*H*), 7.44 (2H, t, *J* = 7.3 Hz, Ar*H*), 7.41 – 7.30 (5H, m, Ar*H*), 5.37 (1H, dd, *J* = 8.2, 9.8 Hz, PhC*H*), 4.50 (1H, dd, *J* = 9.8, 11.0 Hz, CH*H*), 3.95 (1H, dd, *J* = 8.2, 11.0 Hz, CH*H*), 2.84 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$): 159.4 (C), 141.5 (C), 131.3 (CH), 129.8 (C), 129.5 (CH),

128.9 (CH), 128.1 (CH), 127.9 (CH), 126.5 (CH), 68.0 (CH), 58.0 (CH_2), 40.0 (CH_3); *m/z* (ES^+) 301 $[MH]^+$; HRMS (ES^+) calcd. for $C_{16}H_{17}N_2O_2S$ $[MH]^+$: 301.1005, found: 301.1009.



307

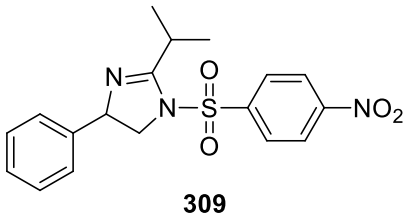
2-(*tert*-Butyl)-1-(methylsulfonyl)-4-phenyl-4,5-dihydro-1*H*-imidazole, 307. Using aziridine **269** (99 mg, 0.50 mmol), $BF_3{\cdot}OEt_2$ (309 μL, 2.50 mmol), ^{t}BuCN (208 mg, 2.50 mmol), imidazoline **307** (67 mg, 48%) was produced as a clear oil. IR (film): 1621, 1347 (S=O), 1168 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.36 (2H, t, *J* = 7.5 Hz, Ar*H*), 7.29 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.22 (2H, d, *J* = 7.5 Hz, Ar*H*), 5.10 (1H, dd, *J* = 7.5, 9.7 Hz, PhC*H*), 4.31 (1H, dd, *J* = 9.7, 10.7 Hz, CH*H*), 3.74 (1H, dd, *J* = 7.5, 10.7 Hz, CH*H*), 2.94 (3H, s, SO_2CH_3), 1.49 (9H, s, $C(CH_3)_3$); δ_C (125 MHz, $CDCl_3$): 166.7 (C), 141.8 (C), 128.8 (CH), 127.8 (CH), 126.3 (CH), 65.9 (CH), 58.8 (CH_2), 39.5 (CH_3), 36.5 (C), 29.0 (CH_3); *m/z* (ES^+) 281 $[MH]^+$; HRMS (ES^+) calcd. for $C_{14}H_{21}N_2O_2S$ $[MH]^+$: 281.1318, found: 281.1321.



308

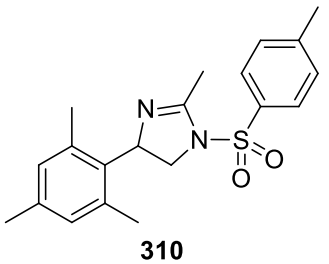
2–Methyl–1–(4–nitrobenzenesulfonyl)–4–phenyl-4,5–dihydro–1*H*–imidazole, 308. Using aziridine **268** (152 mg, 0.50 mmol), $BF_3{\cdot}OEt_2$ (309 μL, 2.50 mmol), MeCN (131 μL, 2.51 mmol), imidazoline **308** (117 mg, 68%) was synthesized as a clear oil. IR (film): 1651, 1531 (C=C), 1350 (S=O), 1171 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.38 (2H, d, *J* = 8.9 Hz, Ar*H*), 8.04 (2H, d, *J* = 8.9 Hz, Ar*H*), 7.29 – 7.23 (3H, m, Ar*H*), 7.08 – 7.03 (2H, m, Ar*H*), 5.09 – 5.03 (1H, m, PhC*H*), 4.22 (1H, t, *J* = 10.0 Hz, CH*H*), 3.66 (1H, dd, *J* = 7.6, 10.0 Hz, CH*H*), 2.43 – 2.41 (3H, m, CH_3); δ_C (125 MHz, $CDCl_3$): 155.3 (C), 150.6 (C), 143.9 (C), 141.1 (C), 128.9 (CH), 128.4 (CH), 127.9 (CH), 126.2 (CH), 124.8 (CH), 66.8 (CH),

55.7 (CH_2), 17.0 (CH_3); *m/z* (ES^+) 346 $[MH]^+$; HRMS (ES^+) calcd. for $C_{16}H_{16}N_3O_4S$ $[MH]^+$: 346.0856, found: 346.0856. Data consistent with that reported in literature.[284]



309

2-Isopropyl-1-(4-nitrobenzenesulfonyl)-4-phenyl-4,5-dihydro-1*H*-imidazole, 309. Using aziridine **268** (152 mg, 0.50 mmol), $BF_3{\cdot}OEt_2$ (309 μL, 2.50 mmol), ^{i}PrCN (173 mg, 2.50 mmol), imidazoline **309** (151 mg, 81%) was synthesized as a clear oil. IR (film): 1642, 1531 (C=C), 1350 (S=O), 1171 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.32 (2H, d, *J* = 8.9 Hz, Ar*H*), 7.96 (2H, d, *J* = 8.9 Hz, Ar*H*), 7.24 – 7.20 (3H, m, Ar*H*), 7.00 – 6.94 (2H, m, Ar*H*), 5.03 (1H, dd, *J* = 6.7, 10.2 Hz, PhC*H*), 4.19 (1H, t, *J* = 10.2 Hz, CH*H*), 3.65 (1H, dd, *J* = 6.7, 10.2 Hz, CH*H*), 3.38 (1H, sep, *J* = 6.5 Hz, C*H*Me_2), 1.35 (3H, d, *J* = 6.5 Hz, CH_3), 1.33 (3H, d, *J* = 6.5 Hz, CH_3); δ_C (125 MHz, $CDCl_3$): 164.5 (C), 150.5 (C), 143.8 (C), 141.7 (C), 128.7 (CH), 128.3 (CH), 127.7 (CH), 126.0 (CH), 124.7 (CH), 66.4 (CH), 56.3 (CH_2), 28.9 (CH), 21.4 (CH_3), 21.2 (CH_3); *m/z* (ES^+) 374 $[MH]^+$; HRMS (ES^+) calcd. for $C_{18}H_{20}N_3O_4S$ $[MH]^+$: 374.1169, found: 374.1173.



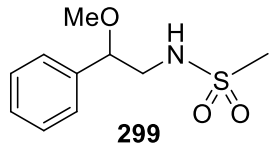
310

4-Mesityl-2-methyl-1-(4-methylbenzenesulfonyl)-4,5-dihydro-1*H*-imidazole, 310. Using aziridine **273** (158 mg, 0.50 mmol), $BF_3{\cdot}OEt_2$ (309 μL, 2.50 mmol), MeCN (131 μL, 2.51 mmol), imidazoline **310** (94 mg, 53%) was synthesized as a clear oil. IR (film): 2916 (C–H) 1648, 1355 (S=O), 1163 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.79 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.36 (2H, d, *J* = 8.4 Hz, Ar*H*), 6.75 (2H, s, Ar*H*), 5.43 – 5.35 (1H, m, ArC*H*), 4.11 (1H, dd, *J* = 9.6, 11.2 Hz, CH*H*), 3.54 (1H, dd, *J* = 9.6, 10.6 Hz, CH*H*), 2.46 (3H, s, ArCH_3), 2.39 – 2.36 (3H, m,

C*H*$_3$), 2.21 (3H, s, ArC*H*$_3$), 2.04 (6H, s, ArC*H*$_3$); δ_C (125 MHz, $CDCl_3$): 155.4 (C), 144.7 (C), 137.1 (C), 136.7 (C), 135.5 (C), 132.8 (C), 130.2 (CH), 130.1 (CH), 127.4 (CH), 63.3 (CH), 52.9 (CH_2), 21.6 (CH_3), 20.7 (CH_3), 20.3 (CH_3), 16.8 (CH_3); *m/z* (ES^+) 357 $[MH]^+$; HRMS (ES^+) calcd. for $C_{20}H_{25}N_2O_2S$ $[MH]^+$: 357.1631, found: 357.1639.

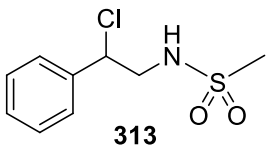
6.10 General method for cascade reactions involving aziridine intermediates from 1,2-amino alcohols.

The 1,2-amino alcohol (0.50 mmol, 1 eq), DBU (2.25 mmol, 4.5 eq) and DMAP (0.25 mmol, 0.5 eq) were dissolved in $CHCl_3$ (2.0 cm^3) to give solution A. Ms_2O (1.25 mmol, 2.5 eq) was dissolved in $CHCl_3/CH_2Cl_2$ (1:1, 2.0 cm^3) to give solution B. Solution C was made by dissolving the nucleophile and catalyst in a suitable solvent (4.0 cm^3); details are given for each entry. These solutions were combined in the three-input microreactor (Figure 6.2). The syringe pump additions were adjusted to give a 16 min residence time for the initial combination of solutions A and B; and a further 12 min residence time upon addition of solution C. The outlet stream was quenched into a stirred solution of saturated aq $NaHCO_3$. Upon completion of the run, additional quantities of $CHCl_3$ were passed through the microreactor to ensure all the product was collected. The resulting mixture was extracted with CH_2Cl_2 (5 × 5 cm^3), the combined organic extracts dried over $MgSO_4$, and solvent removed *in vacuo*. Purification by column chromatography gave the following products:



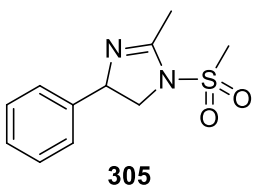
299

***N*-(2-Methoxy-2-phenylethyl)methanesulfonamide, 299.** Using 2-amino-2-phenylethan-1-ol (69 mg, 0.50 mmol), DBU (343 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) to make solution A; Ms_2O (218 mg, 1.25 mmol) to generate solution B; and MsOH (384 mg, 4.0 mmol) in MeOH (4.0 cm^3) to produce solution C, **299** (70 mg, 61%) was produced as a clear oil after work-up and chromatography (1:1 ^{n}hexane:EtOAc). Data as previously described.



313

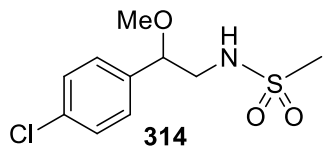
***N*-(2-Chloro-2-phenylethyl)methanesulfonamide, 313.** Using 2-amino-2-phenylethan-1-ol (69 mg, 0.50 mmol), DBU (343 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) to make solution A; Ms_2O (218 mg, 1.25 mmol) to generate solution B; and HCl (2M in Et_2O, 2.0 cm^3) in $CHCl_3$ (2.0 cm^3) to produce solution C, **313** (68 mg, 58%) was produced as a clear oil after work-up and chromatography (1:1; ^{n}hexane:EtOAc). IR (film): 3287 (N−H), 1454 (C=C), 1319 (S=O), 1149 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.43 – 7.34 (5H, m, Ar*H*), 5.03 (1H, dd, *J* = 5.9, 7.8 Hz, PhC*H*), 4.73 – 4.65 (1H, m, N*H*), 3.69 – 3.58 (2H, m, CH_2), 2.91 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$): 137.8 (C), 129.2 (CH), 129.0 (CH), 127.3 (CH), 62.2 (CH), 50.6 (CH_2), 41.3 (CH_3); *m/z* (ES^+) 256, 258 $[MNa]^+$; HRMS (ES^+) calcd. for $C_9H_{12}ClNNaO_2S$ 256.0169, found: 256.0170.



305

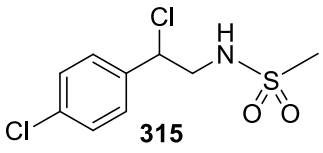
2-Methyl-1-methylsulfonyl-4-phenyl-4,5-dihydro-1*H*-imidazole, 305. Using 2-amino-2-phenylethan-1-ol (69 mg, 0.50 mmol), DBU (343 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) to make solution A; Ms_2O (218 mg, 1.25 mmol) to generate solution B; a solution of 15.2% BF_3 in MeCN solution (1.78 g, 4.0 mmol) was diluted with MeCN to produce 4.0 cm^3 of solution C, **305** (50 mg, 42%) was synthesized as a clear oil

was produced as a clear oil after work-up and chromatography (EtOAc). Data as previously described.



314

***N*-[2-(4-Chlorophenyl)-2-methoxyethyl]methane sulfonamide, 314.** Using 2-amino-2-(4-chloro phenyl)ethan-1-ol (86 mg, 0.50 mmol), DBU (343 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) to make solution A; Ms_2O (218 mg, 1.25 mmol) to generate solution B; and MsOH (384 mg, 4.0 mmol) in MeOH (4.0 cm^3) to produce solution C, **314** (75 mg, 57%) was produced as a clear oil after work-up and chromatography (1:1; ^{n}hexane:EtOAc). IR (film): 3284 (N−H), 1489 (C=C), 1316 (S=O), 1147 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.36 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.26 (2H, d, *J* = 8.5 Hz, Ar*H*), 4.84 – 4.77 (1H, m, ArC*H*), 4.33 (1H, dd, *J* = 3.8, 8.7 Hz, N*H*), 3.36 – 3.30 (1H, m, C*H*H), 3.27 (3H, s, OCH_3), 3.21 – 3.15 (1H, m, CH*H*), 2.93 (3H, s, SO_2CH_3); δ_C (125 MHz, $CDCl_3$): 136.8 (C), 134.3 (C), 129.0 (CH), 128.1 (CH), 82.0 (CH), 57.0 (CH_3), 49.3 (CH_2), 40.6 (CH_3); *m/z* (ES^+) 286, 288 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{10}H_{14}ClNNaO_3S$ $[MNa]^+$: 286.0275, found : 286.0278.

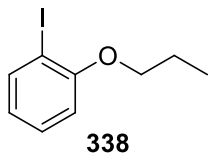


315

***N*-[2-Chloro-2-(4-chlorophenyl)ethyl]methane sulfonamide, 315.** Using 2-amino-2-(4-chloro phenyl)ethan-1-ol (86 mg, 0.50 mmol), DBU (343 mg, 2.25 mmol), DMAP (31 mg, 0.25 mmol) to make solution A; Ms_2O (218 mg, 1.25 mmol) to generate solution B; and HCl (2M in Et_2O, 2.0 cm^3) in $CHCl_3$ (2.0 cm^3) to produce solution C, **315** (71 mg, 53%) was produced as a clear oil after work-up and chromatography (1:1; ^{n}hexane:EtOAc). IR (film): 3264 (N−H), 1493 (C=C), 1147 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.40 – 7.33 (4H, m, Ar*H*), 5.01 (1H, dd, *J* = 5.9, 7.9 Hz, ArC*H*); 4.75 (1H, t, *J* = 6.3 Hz, N*H*), 3.65 – 3.54 (2H, m, CH_2), 2.94 (3H, s,

C*H*$_3$); δ_C (125 MHz, $CDCl_3$): 136.3 (C), 135.1 (C), 129.2 (CH), 128.7 (CH), 61.4 (CH), 50.5 (CH_2), 41.3 (CH_3); *m/z* (ES^+) 290, 292 $[MNa]^+$; HRMS (ES^+) calcd. for $C_9H_{11}Cl_2NNaO_2S$ $[MNa]^+$: 289.9780, found: 289.9783.

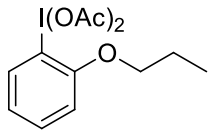
6.11 Synthesis of 1-iodo-2-propoxybenzene, 338.



338

2-iodophenol (2.31 g, 10.5 mmol, 1 eq) was dissolved in DMF (20 cm^3). K_2CO_3 (7.78 g, 56.3 mmol, 5.4 eq) was added, and the mixture stirred for 10 min. 1-iodopropane (2.57 g, 15.1 mmol, 1.4 eq) was added, and the mixture stirred at 50°C for 5 h, at which point, a yellow solution containing solids was obtained. The solvent was removed under high vacuum on a rotary evaporator, saturated aq NaCl (50 cm^3) was added, and the mixture extracted with EtOAc (5 × 10 cm^3). The organic extracts were combined, dried with $MgSO_4$, filtered and the solvent removed *in vacuo*. Column chromatography (5:1 ^{n}hexane:EtOAc) gave **338** (2.20 g, 80%). IR (film): 2963 (C−H), 2935 (C−H), 2875 (C−H), 1580 (C=C) cm^{-1}. δ_H (500 MHz, $CDCl_3$): 7.79 – 7.74 (1H, m, Ar*H*), 7.31 – 7.25 (1H, m, Ar*H*), 6.82 – 6.78 (1H, m, Ar*H*), 6.72 – 6.67 (1H, m, Ar*H*), 3.98 (2H, t, *J* = 7.0 Hz, OC*H*$_2$CH$_2$CH$_3$), 1.87 (2H, sextuplet, *J* = 7.0 Hz, OCH$_2$C*H*$_2$CH$_3$), 1.10 (3H, t, *J* = 7.0 Hz, OCH$_2$CH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$): 157.6 (C), 139.4 (CH), 129.4 (CH), 122.3 (CH), 112.1 (CH), 86.7 (C), 70.7 (CH_2), 22.6 (CH_2), 10.8 (CH_3). Data consistent with that reported in literature.[255]

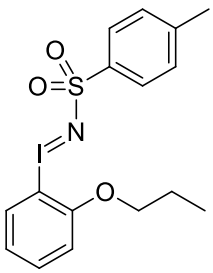
6.12 Synthesis of (2-propoxyphenyl)-λ³-iodanediyl diacetate, 339.



339

To **338** (2.20 g, 8.39 mmol, 1 eq) was added 39% AcOOH in AcOH (3.93 g solution, 1.53 g AcOOH, 20.1 mmol, 2.4 eq) dropwise over 1 hour, and the mixture stirred at 31 °C. The solution turned from orange, then yellow. After complete addition of AcOOH, the temperature was increased to 45 °C, and the mixture stirred for 2 h. The reaction was monitored by ^{1}H NMR spectroscopy. After the signals for **338** had completely disappeared, the excess AcOOH and AcOH were removed at room temperature under high vacuum on a rotary evaporator, giving **339** (2.31 g, 72%) as a pale yellow solid. M.p. 98 – 99 °C (decomposition); (lit. 97.2 – 98 °C). IR (film): 1646, 1275 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.15 – 8.12 (1H, m, Ar*H*), 7.58 – 7.54 (1H, m, Ar*H*), 7.14 – 7.10 (1H, m, Ar*H*), 7.04 – 7.00 (1H, m, Ar*H*), 4.11 (2H, t, *J* = 7.0 Hz, OC*H*$_2$CH$_2$CH$_3$), 1.97 (6H, s, C(O)C*H*$_3$), 1.88 (2H, sextuplet, *J* = 7.0 Hz, OCH$_2$C*H*$_2$CH$_3$), 1.07 (3H, t, *J* = 7.0 Hz, OCH$_2$CH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$): 176.7 (C=O), 155.8 (C), 137.7 (CH), 134.4 (CH), 122.6 (CH), 113.7 (C), 112.8 (CH), 71.2 (CH_2), 22.4 (CH_2), 20.4 (CH_3), 10.6 (CH_3). Data consistent with that reported in literature.[255]

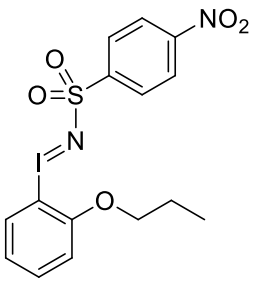
6.13 Synthesis of ArI=NSO$_2$R, 340 – 343.



340

4-Methyl-*N*-[(2-propoxyphenyl)-λ³-iodanylidene]benzene sulfonamide, 40. KOH (150 mg, 2.67 mmol, 2.5 eq) and TsNH$_2$ (182 mg, 1.06 mmol, 1 eq) were dissolved in MeOH (4.1 cm^3), and the solution cooled to 0 °C. **339** (440 mg, 1.16 mmol, 1.09 eq) was added, and the mixture stirred at 0 °C for 2.5 h. The resulting yellow solution was allowed to warm to room temperature over a further 30 min. Then, the solution was added to H_2O (27 cm^3), and a pale yellow precipitate was formed. The mixture was cooled to −78 °C to induce further precipitation.

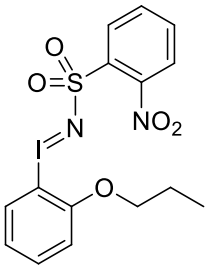
Upon reaching room temperature the precipitate was filtered off, washed with ^{n}hexane (10 cm^3), and dried under high vacuum to give **340** (311 mg, 68%) as a pale yellow powder. M.p. 109 – 110 °C (decomposition); (lit. 96 – 96.4 °C). IR (film): 1579 (C=C), 1170 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.83 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.66 – 7.62 (1H, m, Ar*H*), 7.42 – 7.38 (1H, m, Ar*H*), 7.18 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.09 – 7.04 (1H, m, Ar*H*), 6.90 – 6.86 (1H, m, Ar*H*), 4.05 (2H, t, *J* = 7.1 Hz, OC*H*$_2$CH$_2$CH$_3$), 2.36 (3H, s, ArC*H*$_3$), 1.82 (2H, sextuplet, *J* = 7.1 Hz, OCH$_2$C*H*$_2$CH$_3$), 1.03 (3H, t, *J* = 7.1 Hz, OCH$_2$CH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$): 154.5 (C), 142.0 (C), 140.3 (C), 132.4 (CH), 129.4 (CH), 129.3 (CH), 127.0 (CH), 124.1 (CH), 112.3 (CH), 103.3 (C), 71.6 (CH_2), 22.3 (CH_2), 21.4 (CH_3), 10.8 (CH_3); HRMS (ES$^+$) calcd. for $C_{16}H_{19}INO_3S$ $[MH]^+$: 432.0125, found: 432.0126. Data consistent with that reported in literature.[255]



341

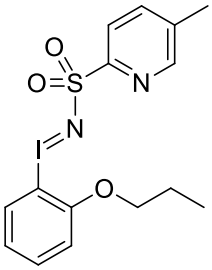
4-Nitro-*N*-[(2-propoxyphenyl)-λ^3-iodanylidene]benzene sulfonamide, 341. KOH (150 mg, 2.67 mmol, 2.5 eq) was dissolved in MeOH (4.1 cm^3), and 4-nitrobenzenesulfon amide (214 mg, 1.06 mmol, 1 eq) added. The mixture was cooled to 0 °C, and **339** (440 mg, 1.16 mmol, 1.09 eq) was added. The mixture was stirred at 0 °C for 2.5 h. The resulting yellow mixture was allowed to warm to room temperature over a further 30 min. The solution was then added to H_2O (27 cm^3), and a pale yellow precipitate was formed. The mixture was cooled to −78 °C to induce further precipitation. Upon reaching room temperature, the precipitate was filtered off, washed with ^{n}hexane (10 cm^3), and dried under high vacuum to give **341** (264 mg, 54%) as a pale yellow powder. M.p. 131 – 132 °C (decomposition). IR (film): 3093 (C–H), 1517, 1347 (S=O), 1121 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.20 (2H, d, *J* = 8.8 Hz, Ar*H*), 8.09 (2H, d, *J* = 8.8 Hz, Ar*H*), 7.59 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.43 (1H, t, *J* = 8.0 Hz, Ar*H*), 7.06 (1H, t, *J* =

8.0 Hz, Ar*H*), 6.90 (1H, d, *J* = 8.0 Hz, Ar*H*), 4.06 (2H, t, *J* = 7.1 Hz, OC*H*$_2$CH$_2$CH$_3$), 1.83 (2H, sextuplet, *J* = 7.1 Hz, OCH$_2$C*H*$_2$CH$_3$), 1.05 (3H, t, *J* = 7.1 Hz, OCH$_2$CH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$): 154.5 (C), 149.23 (C), 149.20 (C), 133.1 (CH), 129.5 (CH), 128.2 (CH), 124.3 (CH), 123.9 (CH), 112.6 (CH), 103.0 (C), 71.6 (CH_2), 22.3 (CH_2), 10.5 (CH_3); HRMS (ES^+) calcd. for $C_{15}H_{15}IN_2NaIO_5S$ $[MNa]^+$: 484.9639, found: 484.9634.



342

2-Nitro-*N*-[(2-propoxyphenyl)-λ^3-iodanylidene]benzene sulfonamide, 342. KOH (150 mg, 2.67 mmol, 2.5 eq) was dissolved in MeOH (4.1 cm^3), and 2-nitrobenzenesulfonamide (214 mg, 1.06 mmol, 1 eq) added. The mixture was cooled to 0 °C, and **339** (440 mg, 1.16 mmol, 1.09 eq) was added. The mixture was stirred at 0 °C for 2.5 h. The resulting yellow mixture was allowed to warm to room temperature over a further 30 min. The solution was then added to H_2O (27 cm^3), and a pale yellow precipitate was formed. The mixture was cooled to −78 °C to induce further precipitation. Upon reaching room temperature, the precipitate was filtered off, washed with ^{n}hexane (10 cm^3), and dried under high vacuum to give **342** (284 mg, 58%) as a pale yellow solid. M.p. 132 – 133 °C (decomposition). IR (film): 3088 (C–H), 2974 (C–H), 2941 (C–H), 2882 (C–H), 1579, 1541, 1365 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.24 – 8.21(1H, m, Ar*H*), 7.85 – 7.81 (1H, m, Ar*H*), 7.64 – 7.55 (3H, m, Ar*H*), 7.47 – 7.41 (1H, m, Ar*H*), 7.19 – 7.14 (1H, m, Ar*H*), 6.95 – 6.91 (1H, m, Ar*H*), 4.09 (2H, t, *J* = 7.0 Hz, OC*H*$_2$CH$_2$CH$_3$), 1.85 (2H, sextuplet, *J* = 7.0 Hz, OCH$_2$C*H*$_2$CH$_3$), 1.05 (3H, t, *J* = 7.0 Hz, OCH$_2$CH$_2$C*H*$_3$); δ_C (125 MHz, $CDCl_3$): 154.4 (C), 147.5 (C), 136.8 (C), 132.6 (CH), 132.1 (CH), 131.8 (CH), 130.7 (CH), 129.0 (CH), 124.5 (CH), 123.7 (CH), 112.4 (CH), 104.5 (C), 71.6 (CH_2), 22.3 (CH_2), 10.5 (CH_3); HRMS (ES^+) calcd. for $C_{15}H_{15}IN_2NaIO_5S$ $[MNa]^+$: 484.9639, found: 484.9639.



343

5-Methyl-*N*-[(2-propoxyphenyl)- λ³-iodanylidene]pyridine -2-sulfonamide, 343. KOH (150 mg, 2.67 mmol, 2.5 eq) and 5-methylpyridine-2-sulfonamide (183 mg, 1.06 mmol, 1 eq) were dissolved in MeOH (4.1 cm^3), and the solution cooled to 0 °C. **339** (440 mg, 1.16 mmol, 1.09 eq) was added, and the mixture stirred at 0 °C for 2.5 h. The resulting yellow solution was allowed to warm to room temperature over a further 30 min. The solution was then added to H_2O (27 cm^3), and a pale yellow precipitate was formed. The mixture was cooled to −78 °C to induce further precipitation. Upon reaching room temperature, the precipitate was filtered off, washed with ^{n}hexane (10 cm^3), and dried under high vacuum to give **343** (280 mg, 61%) as a pale yellow solid. M.p. 127 – 128 °C (decomposition). IR (film): 1585, 1460, 1152 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.40 (1H, s, Ar*H*), 8.00 – 7.96 (1H, m, Ar*H*), 7.93 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.70 – 7.65 (1H, m, Ar*H*), 7.46 – 7.40 (1H, m, Ar*H*), 7.25 – 7.20 (1H, m, Ar*H*), 6.95 – 6.91 (1H, m, Ar*H*), 4.10 (2H, t, *J* = 7.0 Hz, $OCH_2CH_2CH_3$), 2.41 (3H, s, $ArCH_3$), 1.86 (2H, sextuplet, *J* = 7.0 Hz, $OCH_2CH_2CH_3$), 1.07 (3H, *J* = 7.0 Hz, $OCH_2CH_2CH_3$); δ_C (125 MHz, $CDCl_3$): 158.9 (C), 154.5 (C), 148.2 (CH), 138.6 (CH), 135.5 (C), 132.0 (CH), 128.6 (CH), 124.2 (CH), 119.1 (CH), 112.0 (CH), 105.7 (C), 71.3 (CH_2), 22.3 (CH_2), 18.4 (CH_3), 10.6 (CH_3); HRMS (ES^+) calcd. for $C_{15}H_{17}IN_2NaO_3S$ $[MNa]^+$: 454.9897, found: 454.9899.

6.14.1 General method for aziridination of alkenes in flow.

A custom flow system was assembled by connecting computer controlled Tricontinent C3000 syringe pumps to a XXL-S-01 three-input flow reactor purchased from Little Things Factory. As only two inputs A and B were used, the third input C was blocked off; the reactor had a total reaction volume of 4.5 cm^3 (including tubing carrying away solution to thermal quench) when used in this way.

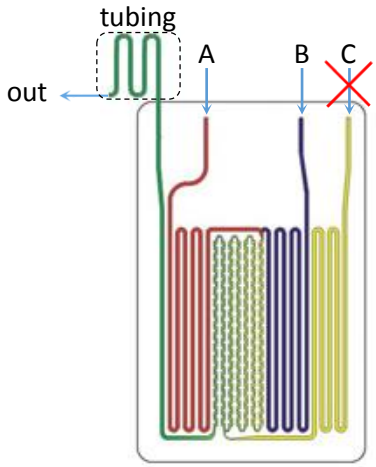
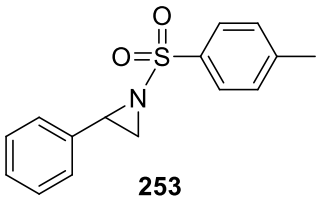


Figure 6.3: Flow reactor used for aziridinations.

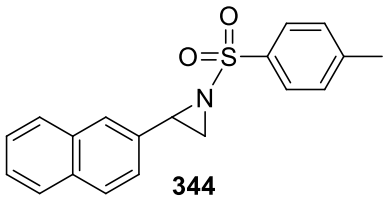
ArI=NSO_2R (0.10 mmol, 1 eq) was dissolved in CH_2Cl_2 (2.0 cm^3) to give solution A; vigorous shaking was sometimes necessary for complete dissolving. Alkene (1.00 mmol, 10 eq for aromatic alkenes and norbornene; 2.00 mmol, 20 eq for cycloheptene) and $(pyr)_4Cu(OTf)_2$ (0.01 mmol, 0.1 eq) were dissolved in anhydrous MeCN (2.0 cm^3) to give solution B. Solutions A and B were combined in the XXL-S-01 microreactor at room temperature, with a residence time of 10 min. The outlet stream was quenched thermally at −78 °C. Upon completion of the run, additional quantities of CH_2Cl_2 and MeCN were passed through the microreactor at A and B respectively to ensure all the product was collected.

The resulting mixture was concentrated under vacuum and purified by gradient column chromatography (5:1 ^{n}hexane:EtOAc, then 3:1 ^{n}hexane:EtOAc) to give the following products:



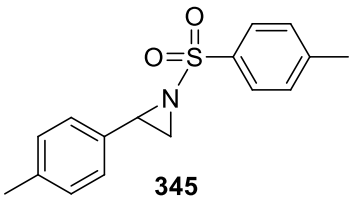
253

2-Phenyl-1-tosylaziridine, 253. Using **340** (44 mg, 0.102 mmol), styrene (105 mg, 1.01 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **253** (23 mg, 82%) was produced as a clear oil. Other data as previously reported.



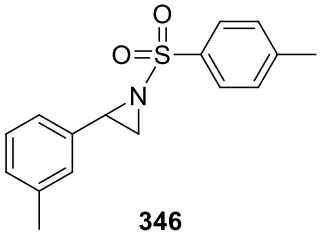
344

2-(Naphthalen-2-yl)-1-tosylaziridine, 344. Using **340** (44 mg, 0.102 mmol), 2-vinyl naphthalene (155 mg, 1.01 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **344** (23 mg, 70%) was produced as a clear oil. IR (film): 1597 (C=C), 1324 (S=O), 1161 (S=O) cm^{-1}; δ_H (500 MHz, CD_2Cl_2): 7.91 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.87 – 7.82 (3H, m, Ar*H*), 7.78 (1H, s, Ar*H*), 7.55 – 7.49 (2H, m, Ar*H*), 7.41 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.34 – 7.30 (1H, m, Ar*H*), 3.93 (1H, dd, *J* = 4.5, 7.2 Hz, ArC*H*), 3.06 (1H, d, *J* = 7.2 Hz, CH*H*), 2.56 (1H, d, *J* = 4.5 Hz, C*H*H), 2.47 (3H, s, ArCH_3); δ_C (125 MHz, CD_2Cl_2): 145.0 (C), 134.9 (C), 133.2 (C), 133.1 (C), 132.6 (C), 129.8 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 126.5 (CH), 126.3 (CH), 126.1 (CH), 123.9 (CH), 41.1 (CH), 36.0 (CH_2), 21.4 (CH_3); *m/z* (ES^+) 346 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{19}H_{17}NNaO_2S$ $[MNa]^+$: 346.0872, found: 346.0875. Data consistent with that published in literature.[19]



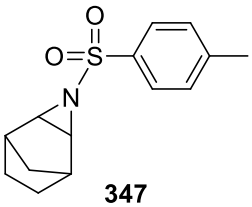
345

2-(*p*-Tolyl)-1-tosylaziridine, 345. Using **340** (44 mg, 0.102 mmol), 4-methylstyrene (119 mg, 1.01 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **345** (20 mg, 68%) was produced as a clear oil. IR (film): 1597 (C=C), 1323 (S=O), 1161 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.88 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.35 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.13 – 7.11 (4H, m, Ar*H*), 3.76 (1H, dd, *J* = 4.5, 7.2 Hz, ArC*H*), 2.99 (1H, d, *J* = 7.2 Hz, CH*H*), 2.45 (3H, s, ArCH_3), 2.40 (1H, d, *J* = 4.5 Hz, C*H*H), 2.33 (3H, s, ArCH_3); δ_C (125 MHz, $CDCl_3$): 144.6 (C), 138.2 (C), 135.1 (C), 132.0 (C), 129.7 (CH), 129.3 (CH), 127.9 (CH), 126.5 (CH), 41.1 (CH), 35.8 (CH_2), 21.7 (CH_3), 21.2 (CH_3); *m/z* (ES^+) 310 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{16}H_{17}NNaO_2S$ $[MNa]^+$: 310.0872, found: 310.0875. Data consistent with that published in literature.[28]



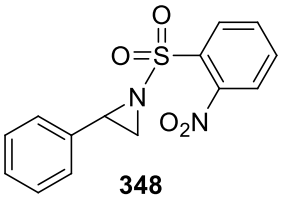
346

2-(*m*-Tolyl)-1-tosylaziridine, 346. Using **340** (44 mg, 0.102 mmol), 3-methylstyrene (119 mg, 1.01 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **346** (20 mg, 68%) was produced as a clear oil. IR (film): 1597 (C=C), 1325 (S=O), 1161 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.87 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.33 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.18 (1H, t, *J* = 7.9 Hz, Ar*H*), 7.08 (1H, d, *J* = 7.9 Hz, Ar*H*), 7.03 – 6.99 (2H, m, Ar*H*), 3.74 (1H, dd, *J* = 4.5, 7.2 Hz, ArC*H*), 2.96 (1H, d, *J* = 7.2 Hz, CH*H*), 2.43 (3H, s, ArCH_3), 2.38 (1H, d, *J* = 4.5 Hz, C*H*H), 2.30 (3H, s, ArCH_3); δ_C (125 MHz, $CDCl_3$): 144.6 (C), 138.3 (C), 135.04 (C), 134.97 (C), 129.8 (CH), 129.1 (CH), 128.5 (CH), 128.0 (CH), 127.2 (CH), 123.7 (CH), 41.1 (CH), 35.9 (CH_2), 21.7 (CH_3), 21.3 (CH_3); *m/z* (ES^+) 310 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{16}H_{17}NNaO_2S[MNa]^+$: 310.0872, found: 310.0867. Data consistent with that published in literature.[28]



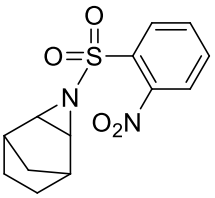
347

3-Tosyl-3-azatricyclo[3.2.1.0^{2,4}]octane, 347. Using **340** (44 mg, 0.102 mmol), norbornene (95 mg, 1.01 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **347** (19 mg, 71%) was produced as a clear oil. IR (film): 2968 (C–H), 2874 (C–H), 1599 (C–H), 1351 (S=O), 1158 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 7.81 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.32 (2H, d, *J* = 8.1 Hz, Ar*H*), 2.92 – 2.91 (2H, m, NC*H*), 2.45 – 2.43 (5H, m, ArCH_3 and RR'R''C*H*), 1.51 – 1.43 (3H, m, R_2CH*H*, CH_2), 1.27 – 1.22 (2H, m, CH_2), 0.77 – 0.73 (1H, m, R_2C*H*H); δ_C (125 MHz, $CDCl_3$): 144.1 (C), 135.9 (C), 129.6 (CH), 127.7 (CH), 42.0 (CH), 35.8 (CH), 28.3 (CH_2), 25.6 (CH_2), 21.6 (CH_3); *m/z* (ES$^+$) 286 [MNa]$^+$; HRMS (ES$^+$) calcd. for $C_{14}H_{17}NNaO_2S$[MNa]$^+$: 286.0872, found: 286.0873. Data consistent with that reported in literature.[255]



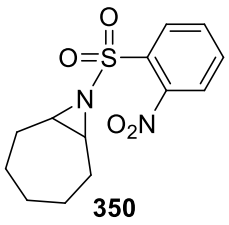
348

1-[(2-Nitrophenyl)sulfonyl]-2-phenylaziridine, 348. Using **342** (47 mg, 0.102 mmol), styrene (105 mg, 1.01 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **348** (24 mg, 77%) was produced as a clear oil. IR (film): 1543 (C=C), 1336 (S=O), 1167 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.26 – 8.23 (1H, m, Ar*H*), 7.78 – 7.72 (3H, m, Ar*H*), 7.36 – 7.29 (5H, m, Ar*H*), 4.04 (1H, dd, *J* = 4.8, 7.2 Hz, ArC*H*), 3.25 (1H, d, *J* = 7.2 Hz, CH*H*), 2.63 (1H, d, *J* = 4.8 Hz, C*H*H); δ_C (125 MHz, $CDCl_3$): 148.6 (C), 134.7 (C), 134.5 (CH), 132.2 (CH), 132.1 (C), 131.3 (CH), 128.7 (CH), 128.6 (CH), 126.6 (CH), 124.5 (CH), 42.9 (CH), 38.1 (CH_2); *m/z* (ES$^+$) 327 [MNa]$^+$; HRMS (ES$^+$) calcd. for $C_{14}H_{12}N_2NaO_4S$ [MNa]$^+$: 327.0410, found: 327.0406. Data consistent with that reported in literature.[19]



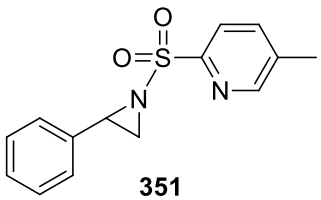
349

3-[(2-Nitrophenyl)sulfonyl]-3-azatricyclo[3.2.1.0^{2,4}]octane, 349. Using **342** (47 mg, 0.102 mmol), norbornene (95 mg, 1.01 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **349** (21 mg, 70%) was produced as a clear oil. IR (film): 2974 (C–H), 2877 (C–H), 1544 (C=C), 1330 (S=O), 1123 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.19 – 8.14 (1H, m, Ar*H*), 7.76 – 7.70 (3H, m, Ar*H*), 3.22 – 3.21 (2H, m, NC*H*), 2.57 – 2.54 (2H, m, RR'R''C*H*), 1.55 – 1.50 (2H, m, CH_2), 1.44 – 1.39 (1H, m, R_2CH*H*), 1.31 – 1.26 (2H, m, CH_2), 0.84 – 0.79 (1H, m, R_2C*H*H); δ_C (125 MHz, $CDCl_3$): 148.4 (C), 134.0 (CH), 132.9 (C), 132.0 (CH), 130.5 (CH), 124.3 (CH), 44.3 (CH), 36.1 (CH), 28.2 (CH_2), 25.4 (CH_2); *m/z* (ES$^+$) 317 [MNa]$^+$; HRMS (ES$^+$) calcd. for $C_{13}H_{14}N_2NaO_4S$ [MNa]$^+$: 317.0566, found: 317.0555.



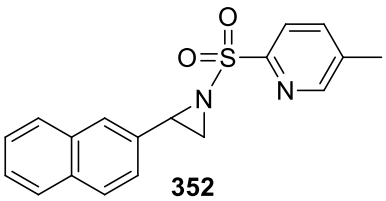
350

8-[(2-Nitrophenyl)sulfonyl]-8-azabicyclo[5.1.0]octane, 350. Using **342** (47 mg, 0.102 mmol), cycloheptene (192 mg, 2.00 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **350** (14 mg, 46%) was produced as a clear oil. IR (film): 2924 (C–H), 2849 (C–H), 1592 (C=C), 1329 (S=O), 1161 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.24 – 8.20 (1H, m, Ar*H*), 7.78 – 7.71 (3H, m, Ar*H*), 3.28 – 3.22 (2H, m, NC*H*), 2.05 – 1.88 (4H, m, CH_2), 1.62 – 1.41 (5H, m, CH_2), 1.26 – 1.16 (1H, m, CH_2); δ_C (125 MHz, $CDCl_3$): 148.5 (C), 134.0 (CH), 133.0 (C), 132.2 (CH), 131.0 (CH), 124.4 (CH), 46.9 (CH), 31.0 (CH_2), 28.2 (CH_2), 25.1 (CH_2); *m/z* (ES$^+$) 319 [MNa]$^+$; HRMS (ES$^+$) calcd. for $C_{13}H_{16}N_2NaO_4S$ [MNa]$^+$: 319.0723, found: 319.0729.



351

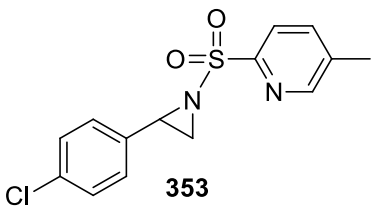
5-Methyl-2-[(2-phenylaziridin-1-yl)sulfonyl] pyridine, 351. Using **343** (44 mg, 0.102 mmol), styrene (105 mg, 1.01 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **351** (22 mg, 79%) was produced as a clear oil. IR (film): 1572 (C=C), 1327 (S=O), 1171 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.57 – 8.55 (1H, m, Ar*H*), 8.02 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.72 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.32 – 7.24 (5H, m, Ar*H*), 4.00 (1H, dd, *J* = 4.7, 7.2 Hz, PhC*H*), 3.20 (1H, d, *J* = 7.2 Hz, CH*H*), 2.51 (1H, d, *J* = 4.7 Hz, C*H*H), 2.44 (3H, s, ArCH_3); δ_C (125 MHz, $CDCl_3$): 153.3 (C), 150.8 (CH), 138.3 (C), 138.2 (CH), 134.9 (C), 128.5 (CH), 128.4 (CH), 126.7 (CH), 122.8 (CH), 41.4 (CH), 36.0 (CH_2), 18.6 (CH_3); *m/z* (ES^+) 297 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{14}H_{14}N_2NaO_2S$ $[MNa]^+$: 297.0668, found: 297.0670. Data consistent with that published in literature.[197]



352

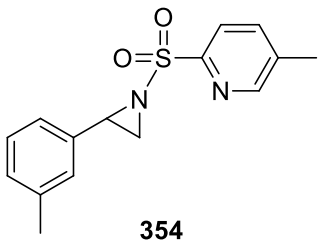
5 - Methyl - 2-[[2-(naphthalen-2-yl)aziridin-1-yl]sulfonyl]pyridine, 352. Using **343** (44 mg, 0.102 mmol), 2-vinylnaphthalene (155 mg, 1.01 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **352** (24 mg, 73%) was produced as a clear oil. IR (film): 3051 (C–H), 1572 (C=C), 1325 (S=O), 1170 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.58 – 8.53 (1H, m, Ar*H*), 8.04 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.81 – 7.76 (4H, m, Ar*H*), 7.73 – 7.69 (1H, m, Ar*H*), 7.49 – 7.44 (2H, m, Ar*H*), 7.34 – 7.30 (1H, m, Ar*H*), 4.15 (1H, dd, *J* = 4.7, 7.2 Hz, ArC*H*), 3.28 (1H, d, *J* = 7.2 Hz, CH*H*), 2.61 (1H, d, *J* = 4.7 Hz, C*H*H), 2.42 (3H, s, ArCH_3); δ_C (125 MHz, $CDCl_3$): 153.9 (C), 150.9 (CH), 138.3 (C), 138.2 (CH), 133.2 (C), 133.1 (C), 132.4 (C), 128.4 (CH), 127.8 (CH), 127.7 (CH), 126.4 (CH), 126.35 (CH), 126.32 (CH), 123.9 (CH), 122.8 (CH), 41.7 (CH), 36.1 (CH_2), 18.6 (CH_3); *m/z* (ES^+) 347 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{18}H_{16}N_2NaO_2S$ $[MNa]^+$: 347.0825, found: 347.0822.

Data consistent with that published in literature.[197]



353

2-[[2-(4-Chlorophenyl)aziridin-1-yl]sulfonyl] -5-methylpyridine, 353. Using **343** (44 mg, 0.102 mmol), 4-chlorostyrene (139 mg, 1.00 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **353** (24 mg, 76%) was produced as a clear oil. IR (film): 1572 (C=C), 1326 (S=O), 1170 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.46 (1H, s, Ar*H*), 7.88 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.66 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.21 (2H, d, *J* = 8.5 Hz, Ar*H*), 7.13 (2H, d, *J* = 8.5 Hz, Ar*H*), 3.83 (1H, dd, *J* = 4.7, 7.1 Hz, ArC*H*), 3.04 (1H, d, *J* = 7.1 Hz, CH*H*), 2.39 (1H, d, *J* = 4.7 Hz, C*H*H), 2.35 (3H, s, ArCH_3); δ_C (125 MHz, $CDCl_3$): 153.4 (C), 151.3 (CH), 139.1 (C), 138.6 (CH), 134.5 (C), 134.3 (C), 129.1 (CH), 128.5 (CH), 123.1 (CH), 40.9 (CH), 36.2 (CH_2), 18.8 (CH_3); *m/z* (ES^+) 331 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{14}H_{13}ClN_2NaO_2S$ $[MNa]^+$: 331.0278, found: 331.0281. Data consistent with that published in literature.[285]



354

5-Methyl-2-[[2-(*m*-tolyl)aziridin-1-yl]sulfonyl] pyridine, 354. Using **343** (44 mg, 0.102 mmol), 3-methylstyrene (119 mg, 1.01 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **354** (24 mg, 82%) was produced as a clear oil. IR (film): 1655 (C=C), 1327 (S=O), 1172 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.57 – 8.55 (1H, m, Ar*H*), 8.02 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.74 – 7.70 (1H, m, Ar*H*), 7.20 – 7.16 (1H, m, Ar*H*), 7.10 – 7.05 (3H, m, Ar*H*), 3.96 (1H, dd, *J* = 4.7, 7.2 Hz, ArC*H*), 3.18 (1H, d, *J* = 7.2 Hz, CH*H*), 2.50 (1H, d, *J* = 4.7 Hz, C*H*H), 2.50 (3H, s, ArCH_3), 2.30 (3H, s, ArCH_3); δ_C (125 MHz, $CDCl_3$): 153.3 (C), 150.8 (CH), 138.3 (C), 138.2 (C), 138.1 (CH), 134.9 (C), 129.1 (CH), 128.4 (CH), 127.3

(CH), 123.9 (CH), 122.8 (CH), 41.3 (CH), 36.1 (CH_2), 21.3 (CH_3), 18.6 (CH_3); *m/z* (ES^+) 311 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{16}N_2NaO_2S$ $[MNa]^+$: 311.0825, found: 311.0824.

6.14.2 Alternative flow synthesis of 344 and 346 in a PTFE tubing flow reactor

A custom flow system was assembled by connecting computer controlled Tricontinent C3000 syringe pumps to a custom built flow reactor constructed out of 1/16" ID PTFE tubing and a T-mixer (Figure 6.4).

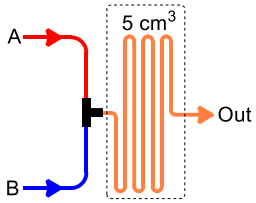
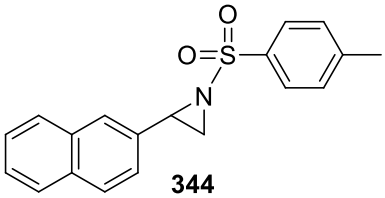


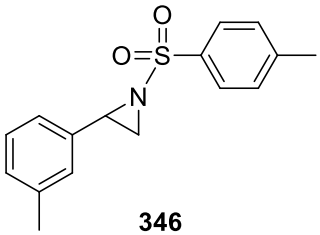
Figure 6.4. Schematic of the flow reactor used for aziridinations.

340 (0.10 mmol, 1 eq) was dissolved in CH_2Cl_2 (2.0 cm^3) to give solution A. Alkene (1.00 mmol, 10 eq) and $(pyr)_4Cu(OTf)_2$ (0.01 mmol, 0.1 eq) were dissolved in anhydrous MeCN (2.0 cm^3) to give solution B. Solutions A and B were combined in the tube reactor at room temperature, with a residence time of 10 min. The outlet stream was quenched thermally at −78 °C. Upon completion of the run, additional quantities of CH_2Cl_2 and MeCN were passed through the tube reactor at A and B respectively to ensure all the product was collected. The resulting mixure was concentrated under vacuum and purified by gradient column chromatography (5:1 ^{n}hexane:EtOAc, then 3:1 ^{n}hexane:EtOAc) to give the following products:



344

2-(Naphthalen-2-yl)-1-tosylaziridine, 344. Using **340** (44 mg, 0.102 mmol), 2-vinyl naphthalene (155 mg, 1.01 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **344** (24 mg, 73%) was produced as a clear oil. Other data as previously reported.



346

2-(*m*-Tolyl)-1-tosylaziridine, 346. Using **340** (44 mg, 0.102 mmol), 3-methylstyrene (119 mg, 1.01 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol), **346** (20 mg, 68%) was produced as a clear oil. Other data as previously reported.

6.15 General method for the aziridination of alkenes and subsequent ring opening in flow.

A custom flow system was assembled by connecting computer controlled Tricontinent C3000 syringe pumps to a custom built flow reactor constructed out of 1/16" ID PTFE tubing and T-mixers (Figure 6.5).

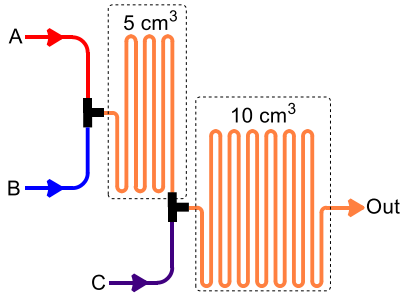
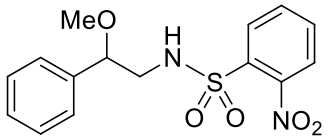


Figure 6.5. Schematic of the flow reactor used for telescoped reactions.

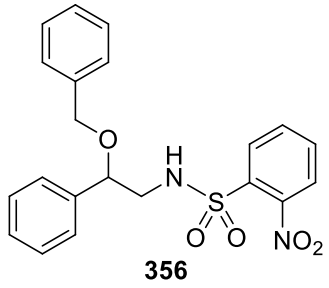
$ArI{=}NSO_2R$ (0.10 mmol, 1 eq) was dissolved in CH_2Cl_2 (2.0 cm^3) to give solution A. Alkene (0.50 mmol, 5.0 eq) and $(pyr)_4Cu(OTf)_2$ (0.01 mmol, 0.1 eq) were dissolved in anhydrous MeCN (2.0 cm^3) to give solution B. Solution C was made by dissolving

the nucleophile and acid in a suitable solvent (4.0 cm^3); details are given for each entry. Solutions A and B were combined in the first section of the flow reactor at room temperature, with a residence time of 10 min. Solution C was then added in the second section of the flow reactor at room temperature, with a residence time of 10 min. The outlet stream was quenched into a solution of NEt_3 (0.50 mmol) in $CHCl_3$ (2 cm^3) for alcohol ring openings, or saturated aq $NaHCO_3$ (5 cm^3) for HCl or MeCN ring openings. Upon completion of the run, additional quantities of CH_2Cl_2 were passed through the flow reactor to ensure all the product was collected. The resulting mixture was concentrated under vacuum and purified by gradient column chromatography (3:1 ^{n}hexane:EtOAc, then 1:1 ^{n}hexane:EtOAc) to give the following products:



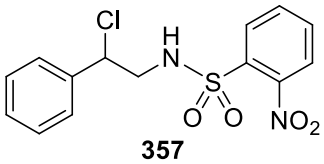
355

***N*–(2–Methoxy–2–phenylethyl)–2–nitrobenzene sulfonamide, 355.** Using **342** (47 mg, 0.102 mmol) to make solution A; styrene (53 mg, 0.509 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; H_2SO_4 (15 mg, 0.153 mmol) in MeOH (4.0 cm^3) to make solution C, **355** (25 mg, 73%) was obtained as a clear oil. IR (film): 3342 (N–H), 2932 (C–H), 1575 (C=C), 1343 (S=O), 1167 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.11 – 8.06 (1H, m, Ar*H*), 7.91 – 7.87 (1H, m, Ar*H*), 7.75 – 7.69 (2H, m, Ar*H*), 7.35 – 7.27 (3H, m, Ar*H*), 7.23 – 7.20 (2H, m, Ar*H*), 5.88 (1H, dd, *J* = 3.0, 8.1 Hz, N*H*), 4.25 (1H, dd, *J* = 3.6, 9.2 Hz, ArC*H*), 3.43 – 3.37 (1H, m, CH*H*), 3.16 (3H, s, OCH_3), 3.15 – 3.10 (1H, m, C*H*H); δ_C (125 MHz, $CDCl_3$): 148.0 (C), 138.0 (C), 134.0 (C), 133.5 (CH), 132.8 (CH), 131.0(CH), 128.7 (CH), 128.5 (CH), 126.6 (CH), 125.4 (CH), 82.0 (CH), 56.8 (CH_3), 50.0 (CH_2); *m/z* (ES^+) 359 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{16}N_2NaO_5S$ $[MNa]^+$: 359.0672, found: 359.0674.



356

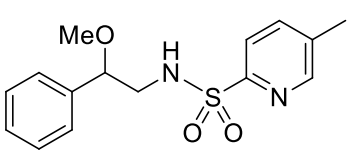
***N*-[2-(Benzyloxy)-2-phenylethyl]-2-nitrobenzene sulfonamide, 356.** Using **342** (47 mg, 0.102 mmol) to make solution A; styrene (53 mg, 0.509 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; MsOH (29 mg, 0.302 mmol) in BnOH (4.0 cm^3) to make solution C, **356** (23 mg, 55%) was obtained as a clear oil. IR (film): 3337 (N–H), 1593 (C=C), 1345 (S=O), 1169 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.09 – 8.05 (1H, m, Ar*H*), 7.87 – 7.82 (1H, m, Ar*H*), 7.73 – 7.66 (2H, m, Ar*H*), 7.40 – 7.25 (10H, m, Ar*H*), 5.92 (1H, dd, *J* = 3.1, 8.3 Hz, N*H*), 4.51 (1H, dd, *J* = 3.6, 9.1 Hz, (BnO)C*H*), 4.44 (1H, d, *J* = 11.4 Hz, OCH*H*Ph), 4.23 (1H, d, *J* = 11.4 Hz, OC*H*HPh), 3.50 – 3.44 (1H, m, CH*H*), 3.27 – 3.21 (1H, m, C*H*H); δ_C (125 MHz, $CDCl_3$): 148.0 (C), 138.1 (C), 137.3 (C), 133.9 (C), 133.4 (CH), 132.7 (CH), 130.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 127.96 (CH), 127.95 (CH), 126.7 (CH), 125.5 (CH), 79.6 (CH), 70.8 (CH_2), 50.0 (CH_2); *m/z* (ES^+) 435 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{21}H_{20}N_2NaO_5S$ $[MNa]^+$: 435.0985, found: 435.0987.



357

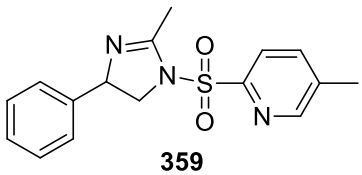
***N*–(2–Chloro–2–phenylethyl)–2–nitrobenzene sulfonamide, 357.** Using **342** (47 mg, 0.102 mmol) to make solution A; styrene (53 mg, 0.509 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; HCl (2M in Et_2O, 1.0 cm^3, 2.0 mmol) in CH_2Cl_2 (3.0 cm^3) to make solution C, **357** (19 mg, 55%) was obtained as a clear oil. IR (film): 3346 (N–H), 1594 (C=C), 1348 (S=O), 1166 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.14 – 8.09 (1H, m, Ar*H*), 7.92 – 7.88 (1H, m, Ar*H*), 7.78 – 7.73 (2H, m, Ar*H*), 7.37 – 7.29 (5H, m, Ar*H*), 5.83 – 5.70 (1H, m, N*H*), 4.95 (1H, dd, *J* = 5.8, 8.1 Hz, ArC*H*), 3.72 – 3.66 (1H, m, CH*H*), 3.63 – 3.57 (1H, m, C*H*H); δ_C (125 MHz, $CDCl_3$): 147.9 (C), 137.5 (C), 134.0 (C), 133.8 (CH), 133.0 (CH), 130.7 (CH),

129.2 (CH), 129.0 (CH), 127.1 (CH), 125.6 (CH), 61.4 (CH), 51.0 (CH_2); *m/z* (ES^+) 363 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{14}H_{13}ClN_2NaO_4S$ $[MNa]^+$: 363.0177, found: 363.0183.



358

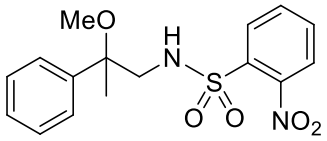
***N*-(2-Methoxy-2-phenylethyl)-5-methylpyridine-2-sulfonamide, 358.** Using **343** (44 mg, 0.102 mmol) to make solution A; styrene (53 mg, 0.509 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; H_2SO_4 (15 mg, 0.153 mmol) in MeOH (4.0 cm^3) to make solution C, **358** (20 mg, 64%) was obtained as a clear oil. IR (film): 3245 (N−H), 1572 (C=C), 1332 (S=O), 1171 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.56 – 8.50 (1H, m, Ar*H*), 7.88 – 7.85 (1H, m, Ar*H*), 7.69 – 7.65 (1H, m, Ar*H*), 7.35 – 7.27 (3H, m, Ar*H*), 7.25 – 7.21 (2H, m, Ar*H*), 5.34 (1H, dd, *J* = 2.8, 9.2 Hz, N*H*), 4.25 (1H, dd, *J* = 3.7, 9.3 Hz, ArC*H*), 3.25 – 3.29 (1H, m, CH*H*), 3.20 (3H, s, OCH_3), 3.13 – 3.06 (1H, m, C*H*H), 2.43 (3H, s, ArCH_3); δ_C (125 MHz, $CDCl_3$): 154.9 (C), 150.6 (CH), 138.3 (C), 138.0 (CH), 137.2 (C), 128.7 (CH), 128.4 (CH), 126.7 (CH), 121.7 (CH), 82.4 (CH), 56.8 (CH_3), 49.8 (CH_2), 18.5 (CH_3); *m/z* (ES^+) 329 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{18}N_2NaO_3S$ $[MNa]^+$: 329.0930, found: 329.0927.



359

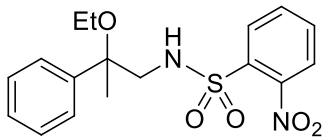
5-Methyl-2-[(2-methyl-4-phenyl-4,5-dihydro-1*H*-imidazol-1-yl)sulfonyl]pyridine, 359. Using **343** (44 mg, 0.102 mmol) to make solution A; styrene (53 mg, 0.509 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; BF_3 (0.23 g of 15% BF_3 in MeCN solution; 0.52 mmol) in MeCN (4.0 cm^3) to make solution C, **359** (23 mg, 71%) was obtained as a clear oil. IR (film): 1651, 1356 (S=O), 1173 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.55 – 8.49 (1H, m, Ar*H*), 7.93

– 7.86 (1H, m, Ar*H*), 7.75 – 7.68 (1H, m, Ar*H*), 7.31 – 7.22 (3H, m, Ar*H*), 7.15 (2H, d, *J* = 7.5 Hz, Ar*H*), 5.09 – 5.01 (1H, m, ArC*H*), 4.27 (1H, t, *J* = 10.0 Hz, CH*H*), 3.70 (1H, dd, *J* = 8.1, 10.0 Hz, C*H*H), 2.46 (3H, s, ArCH_3), 2.45 – 2.44 (3H, m, CH_3); δ_C (125 MHz, $CDCl_3$): 157.2 (C), 153.5 (C), 150.8 (CH), 141.8 (C), 138.3 (CH), 138.2 (C), 128.7 (CH), 127.6 (CH), 126.6 (CH), 122.4 (CH), 67.0 (CH), 56.0 (CH_2), 18.6 (CH_3), 16.9 (CH_3); *m/z* (ES^+) 316 $[MH]^+$; HRMS (ES^+) calcd. for $C_{16}H_{18}N_3O_2S$ $[MH]^+$: 316.1114, found: 316.1116.



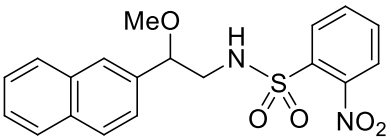
360

***N*-(2-Methoxy-2-phenylpropyl)-2-nitrobenzene sulfonamide, 360.** Using **342** (47 mg, 0.102 mmol) to make solution A; α-methylstyrene (60 mg, 0.508 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; H_2SO_4 (15 mg, 0.153 mmol) in MeOH (4.0 cm^3) to make solution C, **360** (24 mg, 67%) was obtained as a clear oil. IR (film): 3346 (N–H), 1593 (C=C), 1355 (S=O), 1168 (S=O) cm^{-1}; δ_H (500 MHz, CD_2Cl_2): 8.02 – 7.98 (1H, m, Ar*H*), 7.88 – 7.84 (1H, m, Ar*H*), 7.77 – 7.70 (2H, m, Ar*H*), 7.35 – 7.32 (4H, m, Ar*H*), 7.30 – 7.25 (1H, m, Ar*H*), 5.70 – 5.60 (1H, m, N*H*), 3.35 – 3.29 (1H, m, CH*H*), 3.25 – 3.21 (1H, m, C*H*H), 3.07 (3H, s, OCH_3), 1.63 (3H, s, CH_3); δ_C (125 MHz, CD_2Cl_2): 147.8 (C), 141.7 (C), 133.55 (C), 133.46 (CH), 132.8 (CH), 130.9 (CH), 128.4 (CH), 127.7 (CH), 126.1 (CH), 125.2 (CH), 78.1 (C), 54.4 (CH_2), 50.3 (CH_3), 20.3 (CH_3); *m/z* (ES^+) 373 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{16}H_{18}N_2NaO_5S$ $[MNa]^+$: 373.0829, found: 373.0831.



361

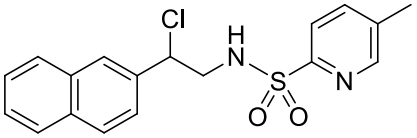
***N*–(2–Ethoxy–2–phenylpropyl)–2–nitrobenzene sulfonamide, 361.** Using **342** (47 mg, 0.102 mmol) to make solution A; α-methylstyrene (60 mg, 0.508 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; H_2SO_4 (15 mg, 0.153 mmol) in EtOH (4.0 cm^3) to make solution C, **361** (21 mg, 56%) was obtained as a clear oil. IR (film): 3350 (N–H), 1593 (C=C), 1352 (S=O), 1169 (S=O) cm^{-1}; δ_H (500 MHz, CD_3CN): 7.99 – 7.95 (1H, m, Ar*H*), 7.89 – 7.85 (1H, m, Ar*H*), 7.83 – 7.76 (2H, m, Ar*H*), 7.39 – 7.30 (4H, m, Ar*H*), 7.29 – 7.24 (1H, m, Ar*H*), 5.94 – 5.71 (1H, m, N*H*), 3.26 – 3.21 (3H, m, CH_2 and OCH*H*), 3.16 – 3.09 (1H, m, OC*H*H), 1.11 (3H, t, *J* = 6.9 Hz, OCH_2CH_3); δ_C (125 MHz, CD_3CN): 148.3 (C), 143.1 (C), 134.4 (CH), 133.4 (CH), 133.2 (C), 130.9 (CH), 128.7 (CH), 127.9 (CH), 126.5 (CH), 125.5 (CH), 78.0 (C), 58.2 (CH_2), 54.1 (CH_2), 21.4 (CH_3), 15.2 (CH_3); *m/z* (ES^+) 387 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{17}H_{20}N_2NaO_5S$ $[MH]^+$: 387.0985, found: 387.0980.



362

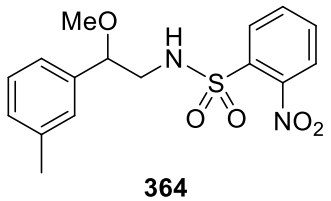
***N*–[2–Methoxy–2–(naphthalene–2–yl)ethyl]–2–nitrobenzenesulfonamide, 362.** Using **342** (47 mg, 0.102 mmol) to make solution A; 2-vinylnaphthalene (78 mg, 0.506 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; H_2SO_4 (15 mg, 0.153 mmol) in MeOH (4.0 cm^3) to make solution C, **362** (28 mg, 71%) was obtained as a clear oil. IR (film): 3351 (N–H), 1594 (C=C), 1343 (S=O), 1167 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.01 – 7.98 (1H, m, Ar*H*), 7.81 – 7.74 (4H, m, Ar*H*), 7.67 (1H, s, Ar*H*), 7.62 – 7.57 (2H, m, Ar*H*), 7.50 – 7.46 (2H, m, Ar*H*), 7.33 – 7.29 (1H, m, Ar*H*), 5.91 (1H, dd, *J* = 3.7, 7.8 Hz, N*H*), 4.43 (1H, dd, *J* = 3.8, 8.5 Hz, ArC*H*), 3.56 – 3.50 (1H, m, CH*H*), 3.31 – 3.25 (1H, m, C*H*H), 3.22 (3H, s, OCH_3); δ_C (125 MHz, $CDCl_3$): 147.8 (C), 135.4 (C), 134.0 (C), 133.4 (C), 133.2 (CH), 133.1 (C), 132.7 (CH), 130.7 (CH), 128.7 (CH), 127.9 (CH), 127.8 (CH), 126.5 (CH),

126.3 (CH), 126.0 (CH), 125.3 (CH), 123.9 (CH), 82.0 (CH), 57.0 (CH_3), 49.9 (CH_2); *m/z* (ES^+) 409 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{19}H_{18}N_2NaO_5S$ $[MNa]^+$: 409.0829, found: 409.0827.



363

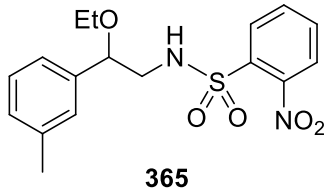
***N*–[2–Chloro–2–(naphthalene–2–yl)ethyl]–5–methylpyridine–2–sulfonamide, 363.** Using **343** (44 mg, 0.102 mmol) to make solution A; 2-vinylnaphthalene (78 mg, 0.506 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; HCl (2M in Et_2O, 1.0 cm^3, 2.0 mmol) in CH_2Cl_2 (3.0 cm^3) to make solution C, **363** (18 mg, 49%) was obtained as a crystalline solid. M.p. 131 – 132 °C. IR (film): 3276 (N–H), 1601 (C=C), 1333 (S=O), 1170 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.43 – 8.38 (1H, m, Ar*H*), 7.86 – 7.83 (1H, m, Ar*H*), 7.83 – 7.77 (4H, m, Ar*H*), 7.65 – 7.60 (1H, m, Ar*H*), 7.53 – 7.48 (2H, m, Ar*H*), 7.46 – 7.42 (1H, m, Ar*H*), 5.53 – 5.45 (1H, m, N*H*), 5.18 (1H, dd, *J* = 6.5, 7.8 Hz, ArC*H*), 3.78 – 3.71 (1H, m, CH*H*), 3.70 – 3.63 (1H, m, C*H*H), 2.37 (3H, s, ArCH_3); δ_C (125 MHz, $CDCl_3$): 154.7 (C), 150.5 (CH), 138.1 (CH), 137.4 (C), 135.1 (C), 133.4 (C), 132.9 (C), 128.9 (CH), 128.1 (CH), 127.7 (CH), 127.0 (CH), 126.8 (CH), 126.7 (CH), 124.3 (CH), 121.7 (CH), 62.1 (CH), 50.7 (CH_2), 18.5 (CH_3); *m/z* (ES^+) 383 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{18}H_{17}ClN_2NaO_2S$ $[MNa]^+$: 383.0591, found: 383.0593.



364

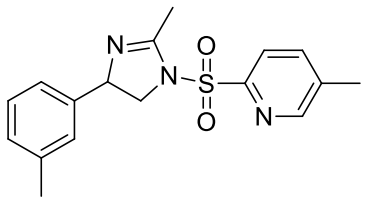
***N*-[2-Methoxy-2-(*m*-tolyl)ethyl]-2-nitrobenzene sulfonamide, 364.** Using **342** (47 mg, 0.102 mmol) to make solution A; 3-methylstyrene (60 mg, 0.508 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; H_2SO_4 (15 mg, 0.153 mmol) in MeOH (4.0 cm^3) to make solution C, **364** (27 mg, 76%) was obtained as a clear oil. IR (film): 3341 (N–H), 1593 (C=C),

1345 (S=O), 1167 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.11 – 8.07 (1H, m, Ar*H*), 7.91 – 7.86 (1H, m, Ar*H*), 7.75 – 7.69 (2H, m, Ar*H*), 7.21 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.10 (1H, d, *J* = 7.5 Hz, Ar*H*), 7.03 – 6.99 (2H, m, Ar*H*), 5.87 (1H, dd, *J* = 2.8, 8.3 Hz, N*H*), 4.21 (1H, dd, *J* = 3.5, 9.2 Hz, ArC*H*), 3.42 – 3.36 (1H, m, CH*H*), 3.15 (3H, s, OCH_3), 3.15 – 3.09 (1H, m, C*H*H), 2.32 (3H, s, ArCH_3); δ_C (125 MHz, $CDCl_3$):148.0 (C), 138.5 (C), 138.0 (C), 134.0 (C), 133.4 (CH), 132.8 (CH), 131.0 (CH), 129.3 (CH), 128.7 (CH), 127.2 (CH), 125.4 (CH), 123.6 (CH), 82.0 (CH), 56.8 (CH_3), 50.0 (CH_2), 21.4 (CH_3); *m/z* (ES^+) 373 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{16}H_{18}N_2NaO_5S$ $[MNa]^+$: 373.0829, found: 373.0830.



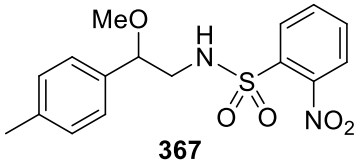
365

***N*–[2–Ethoxy–2–(*m*–tolyl)ethyl]–2–nitrobenzene sulfonamide, 365.** Using **342** (47 mg, 0.102 mmol) to make solution A; 3-methylstyrene (60 mg, 0.508 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; H_2SO_4 (15 mg, 0.153 mmol) in EtOH (4.0 cm^3) to make solution C, **365** (29 mg, 78%) was obtained as a clear oil. IR (film): 3346 (N–H), 1593 (C=C), 1361 (S=O), 1169 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.12 – 8.06 (1H, m, Ar*H*), 7.92 – 7.86 (1H, m, Ar*H*), 7.76 – 7.69 (2H, m, Ar*H*), 7.20 (1H, t, *J* = 7.4 Hz, Ar*H*), 7.09 (1H, d, *J* = 7.4 Hz, Ar*H*), 7.04 – 7.00 (2H, m, Ar*H*), 5.93 (1H, dd, *J* = 3.5, 9.3 Hz, N*H*), 4.32 (1H, dd, *J* = 3.5, 9.3 Hz, ArC*H*), 3.43 – 3.35 (2H, m, OCH*H* and CH*H*), 3.26 – 3.18 (1H, m, OC*H*H), 3.12 – 3.06 (1H, m, C*H*H), 2.32 (3H, s, ArCH_3), 1.13 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); δ_C (125 MHz, $CDCl_3$): 148.1 (C), 138.6 (C), 138.4 (C), 133.9 (C), 133.5 (CH), 132.7 (CH), 131.0 (CH), 129.1 (CH), 128.6 (CH), 127.1 (CH), 125.4 (CH), 123.5 (CH), 80.0 (CH), 64.6 (CH_2), 50.1 (CH_2), 21.4 (CH_3), 15.1 (CH_3); *m/z* (ES^+) 387 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{17}H_{20}N_2NaO_5S$ $[MNa]^+$: 387.0985, found: 387.0983.



366

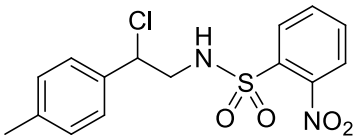
5-Methyl-2-[[2-methyl-4-(*m*-tolyl)-4,5-dihydro-1*H*-imidazol-1-yl]sulfonyl]pyridine, 366. Using **343** (44 mg, 0.102 mmol) to make solution A; 3-methylstyrene (60 mg, 0.508 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; BF_3 (0.23 g of 15% BF_3 in MeCN solution; 0.52 mmol) in MeCN (4.0 cm^3) to make solution C, **366** (26 mg, 77%) was obtained as a clear oil. IR (film): 1650, 1356 (S=O), 1174 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.55 – 8.51 (1H, m, Ar*H*), 7.92 – 7.87 (1H, m, Ar*H*), 7.74 – 7.69 (1H, m, Ar*H*), 7.17 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.05 (1H, d, *J* = 7.7 Hz, Ar*H*), 6.96 – 6.91(2H, m, Ar*H*), 5.05 – 4.97 (1H, m, ArC*H*), 4.25 (1H, t, *J* = 10.0 Hz, CH*H*), 3.69 (1H, dd, *J* = 8.0, 10.0 Hz, C*H*H), 2.46 (3H, s, ArCH_3), 2.45 – 2.44 (3H, m, CH_3), 2.29 (3H, s, ArCH_3); δ_C (125 MHz, $CDCl_3$): 157.1 (C), 153.5 (C), 150.8 (CH), 141.7 (C), 138.3 (C), 138.2 (CH), 138.1 (C), 128.5 (CH), 128.3 (CH), 127.2 (CH), 123.7 (CH), 122.5 (CH), 67.0 (CH), 55.9 (CH_2), 21.4 (CH_3), 18.6 (CH_3), 16.9 (CH_3); *m/z* (ES^+) 330 $[MH]^+$; HRMS (ES^+) calcd. for $C_{17}H_{20}N_3O_2S$ $[MH]^+$: 330.1271, found: 330.1275.



367

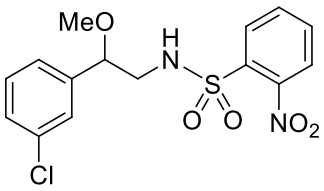
***N*-[2-Methoxy-2-(*p*-tolyl)ethyl]-2-nitrobenzene sulfonamide, 367.** Using **342** (47 mg, 0.102 mmol) to make solution A; 4-methylstyrene (60 mg, 0.508 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; H_2SO_4 (15 mg, 0.153 mmol) in MeOH (4.0 cm^3) to make solution C, **367** (26 mg, 73%) was obtained as a clear oil. IR (film): 3345 (N–H), 1593 (C=C), 1344 (S=O), 1167 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.10 – 8.05 (1H, m, Ar*H*), 7.90 – 7.86 (1H, m, Ar*H*), 7.75 – 7.68 (2H, m, Ar*H*), 7.13 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.09 (2H, d, *J* = 8.2 Hz, Ar*H*), 5.86 (1H, dd, *J* = 3.0, 8.3 Hz, N*H*), 4.21 (1H, dd, *J* = 3.6, 9.1 Hz, ArC*H*), 3.41 – 3.35 (1H, m, CH*H*), 3.16 – 3.09 (1H, m, C*H*H), 3.14 (3H, s, OCH_3), 2.33 (3H, s, ArCH_3); δ_C (125

MHz, $CDCl_3$): 148.0 (C), 138.3 (C), 135.0 (C), 134.0 (C), 133.4 (CH), 132.8 (CH), 131.0 (CH), 129.4 (CH), 126.5 (CH), 125.4 (CH), 81.7 (CH), 56.7 (CH_3), 50.0 (CH_2), 21.2 (CH_3); *m/z* (ES^+) 373 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{16}H_{18}N_2NaO_5S$ $[MNa]^+$: 373.0829, found: 373.0830.



368

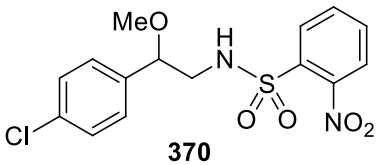
***N*-[2-Chloro-2-(*p*-tolyl)ethyl]-2-nitrobenzene sulfonamide, 368.** Using **342** (47 mg, 0.102 mmol) to make solution A; 4-methylstyrene (60 mg, 0.508 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; HCl (2M in Et_2O, 1.0 cm^3, 2.0 mmol) in CH_2Cl_2 (3.0 cm^3) to make solution C, **368** (21 mg, 58%) was obtained as a clear oil. IR (film): 3342 (N–H), 1593 (C=C), 1348 (S=O), 1166 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.13 – 8.08 (1H, m, Ar*H*), 7.92 – 7.87 (1H, m, Ar*H*), 7.78 – 7.72 (2H, m, Ar*H*), 7.18 (2H, d, *J* = 8.2 Hz, Ar*H*), 7.13 (2H, d, *J* = 8.2 Hz, Ar*H*), 5.80 – 5.67 (1H, m, N*H*), 4.92 (1H, dd, *J* = 5.9, 8.0 Hz, ArC*H*), 3.71 – 3.64 (1H, m, CH*H*), 3.63 – 3.56 (1H, m, C*H*H), 2.33 (3H, s, ArCH_3); δ_C (125 MHz, $CDCl_3$): 147.9 (C), 139.2 (C), 134.5 (C), 134.0 (C), 133.7 (CH), 133.0 (CH), 130.7 (CH), 129.6 (CH), 127.0 (CH), 125.6 (CH), 61.3 (CH), 51.0 (CH_2), 21.2 (CH_3); *m/z* (ES^+) 377 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{15}ClN_2NaO_4S$ $[MNa]^+$: 377.0333, found: 377.0334.



369

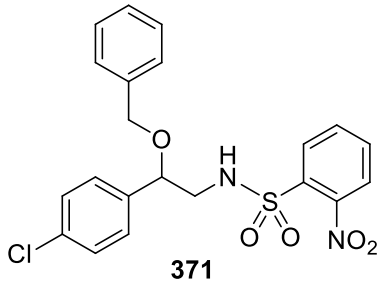
***N*-[2-(3-Chlorophenyl)-2-methoxyethyl]-2-nitro benzenesulfonamide, 369.** Using **342** (47 mg, 0.102 mmol) to make solution A; 3-chlorostyrene (70 mg, 0.505 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; H_2SO_4 (30 mg, 0.306 mmol) in MeOH (4.0 cm^3) to make solution C, **369** (18 mg, 48%) was obtained as a clear oil. IR (film): 3347

(N–H), 1595 (C=C), 1345 (S=O), 1165 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.10 – 8.05 (1H, m, Ar*H*), 7.93 – 7.89 (1H, m, Ar*H*), 7.81 – 7.75 (2H, m, Ar*H*), 7.34 – 7.29 (2H, m, Ar*H*), 7.27 – 7.24 (1H, m, Ar*H*), 7.20 – 7.15 (1H, m, Ar*H*), 5.83 (1H, dd, *J* = 3.4, 7.5 Hz, N*H*), 4.26 (1H, dd, *J* = 3.6, 8.7 Hz, ArC*H*), 3.48 – 3.41 (1H, m, CH*H*), 3.22 – 3.15 (1H, m, C*H*H), 3.19 (3H, s, OCH_3); δ_C (125 MHz, $CDCl_3$): 147.9 (C), 140.5 (C), 134.5 (C), 133.7 (CH), 133.6 (C), 132.9 (CH), 130.8 (CH), 130.0 (CH), 128.5 (CH), 126.6 (CH), 125.4 (CH), 125.0 (CH), 81.2 (CH), 56.9 (CH_3), 49.7 (CH_2); *m/z* (ES^+) 393 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{15}ClN_2NaO_5S$ $[MNa]^+$: 393.0282, found: 393.0284.



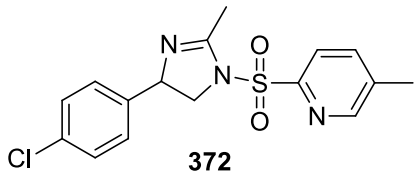
370

***N*-[2-(4-Chlorophenyl)-2-methoxyethyl]-2-nitrobenzenesulfonamide, 370.** Using **342** (47 mg, 0.102 mmol) to make solution A; 4-chlorostyrene (70 mg, 0.505 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; H_2SO_4 (15 mg, 0.153 mmol) in MeOH (4.0 cm^3) to make solution C, **370** (30 mg, 79%) was obtained as a clear oil. IR (film): 3344 (N–H), 1595 (C=C), 1345 (S=O), 1166 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.06 – 8.02 (1H, m, Ar*H*), 7.90 – 7.86 (1H, m, Ar*H*), 7.76 – 7.68 (2H, m, Ar*H*), 7.27 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.16 (2H, d, *J* = 8.4 Hz, Ar*H*), 5.85 (1H, dd, *J* = 3.5, 8.0 Hz, N*H*), 4.24 (1H, dd, *J* = 3.6, 8.7 Hz, ArC*H*), 3.44 – 3.36 (1H, m, CH*H*), 3.16 (3H, s, OCH_3), 3.16 – 3.09 (1H, m, C*H*H); δ_C (125 MHz, $CDCl_3$): 148.0 (C), 136.6 (C), 134.3 (C), 134.0 (C), 133.5 (CH), 132.8 (CH), 130.9 (CH), 128.9 (CH), 127.9 (CH), 125.4 (CH), 81.4 (CH), 56.9 (CH_3), 49.8 (CH_2); *m/z* (ES^+) 393 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{15}ClN_2NaO_5S$ $[MNa]^+$: 393.0282, found: 393.0284.



371

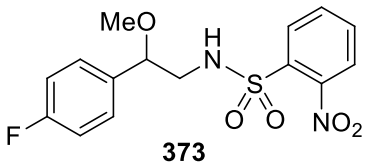
***N*-[2-(Benzyloxy)-2-(4-chlorophenyl)ethyl]-2-nitrobenzenesulfonamide, 371.** Using **342** (47 mg, 0.102 mmol) to make solution A; 4-chlorostyrene (70 mg, 0.505 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; MsOH (29 mg, 0.302 mmol) in BnOH (4.0 cm^3) to make solution C, **371** (28 mg, 61%) was obtained as a clear oil. IR (film): 3362 (N–H), 1595 (C=C), 1345 (S=O), 1168 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.03 – 7.98 (1H, m, Ar*H*), 7.85 – 7.80 (1H, m, Ar*H*), 7.72 – 7.63 (2H, m, Ar*H*), 7.37 – 7.28 (5H, m, Ar*H*), 7.25 – 7.19 (4H, m, Ar*H*), 5.87 (1H, dd, *J* = 3.7, 8.0 Hz, N*H*), 4.48 (1H, dd, *J* = 3.7, 8.5 Hz, ArC*H*), 4.41 (1H, d, *J* = 11.4 Hz, OCH*H*), 4.22 (1H, d, *J* = 11.4 Hz, OC*H*H), 3.47 – 3.41 (1H, m, CH*H*), 3.24 – 3.18 (1H, m, C*H*H); δ_C (125 MHz, $CDCl_3$): 148.0 (C), 137.0 (C), 136.7 (C), 134.4 (C), 133.9 (C), 133.4 (CH), 132.8 (CH), 130.7 (CH), 129.0 (CH), 128.6 (CH), 128.10 (CH), 128.09 (CH), 127.9 (CH), 125.4 (CH), 78.9 (CH), 70.9 (CH_2), 49.9 (CH_2); *m/z* (ES^+) 469 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{21}H_{19}ClN_2NaO_5S$ $[MNa]^+$: 469.0595, found: 469.0599.



372

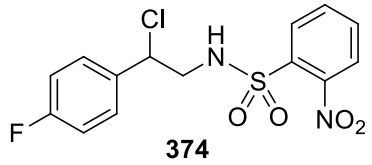
5-Methyl-2-[[4-(4-chlorophenyl)-2-methyl-4,5-dihydro-1*H*-imidazol-1-yl]sulfonyl]pyridine, 372. Using **343** (44 mg, 0.102 mmol) to make solution A; 4-chlorostyrene (70 mg, 0.505 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; BF_3 (0.23 g of 15% BF_3 in MeCN solution; 0.52 mmol) in MeCN (4.0 cm^3) to make solution C, **372** (25 mg, 70%) was obtained as a clear oil. IR (film): 1650, 1356 (S=O), 1172 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.52 – 8.48 (1H, m, Ar*H*), 7.91 – 7.87 (1H, m, Ar*H*), 7.74 – 7.69 (1H, m, Ar*H*), 7.26 (2H, d, *J* = 8.4 Hz, Ar*H*), 7.09 (2H, d, *J* = 8.4 Hz, Ar*H*), 5.06 – 5.00

(1H, m, ArC*H*), 4.27 (1H, t, *J* = 10.0 Hz, CH*H*), 3.66 (1H, dd, *J* = 7.9, 10.0 Hz, C*H*H), 2.46 (3H, s, ArCH_3), 2.44 – 2.42 (3H, m, CH_3); δ_C (125 MHz, $CDCl_3$): 157.7 (C), 153.5 (C), 150.7 (CH), 140.4 (C), 138.32 (CH), 138.29 (C), 133.4 (C), 128.8 (CH), 128.0 (CH), 122.4 (CH), 66.3 (CH), 56.0 (CH_2), 18.6 (CH_3), 16.9 (CH_3); *m/z* (ES^+) 350 $[MH]^+$; HRMS (ES^+) calcd. for $C_{16}H_{17}ClN_3O_2S$ $[MNa]^+$: 350.0725, found: 350.0726.



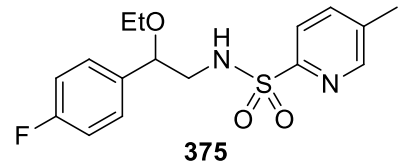
373

***N*–[2–(4–Fluorophenyl)–2–methoxyethyl]–2–nitrobenzenesulfonamide, 373.** Using **342** (47 mg, 0.102 mmol) to make solution A; 4-fluorostyrene (62 mg, 0.508 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; H_2SO_4 (15 mg, 0.153 mmol) in MeOH (4.0 cm^3) to make solution C, **373** (28 mg, 77%) was obtained as a clear oil. IR (film): 3345 (N–H), 1605 (C=C), 1344 (S=O), 1114 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.09 – 8.05 (1H, m, Ar*H*), 7.91 – 7.86 (1H, m, Ar*H*), 7.76 – 7.69 (2H, m, Ar*H*), 7.20 (2H, dd, *J* = 5.4, 8.6 Hz, Ar*H*), 7.01 (2H, t, *J* = 8.6 Hz, Ar*H*), 5.85 (1H, dd, *J* = 3.1, 8.3 Hz, N*H*), 4.24 (1H, dd, *J* = 3.7, 8.9 Hz, ArC*H*), 3.41 – 3.35 (1H, m, CH*H*), 3.15 (3H, s, OCH_3), 3.14 – 3.09 (1H, m, C*H*H); δ_C (125 MHz, $CDCl_3$): 162.7 (d, *J* = 249.0 Hz, (CF)), 148.0 (C), 134.0 (C), 133.8 (d, *J* = 3.0 Hz, (C)), 133.5 (CH), 132.8 (CH), 130.9 (CH), 128.3 (d, *J* = 8.3 Hz, (CH)), 125.4 (CH), 115.7 (d, *J* = 22.1 Hz, (CH)), 81.3 (CH), 56.8 (CH_3), 49.9 (CH_2); *m/z* (ES^+) 377 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{15}H_{15}FN_2NaO_5S$ $[MNa]^+$: 377.0578, found: 377.0574.



374

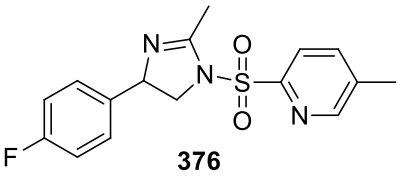
***N*-[2-Chloro-2-(4-fluorophenyl)ethyl]-2-nitro benzenesulfonamide, 374.** Using **342** (47 mg, 0.102 mmol) to make solution A; 4-fluorostyrene (62 mg, 0.508 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; HCl (2M in Et_2O, 1.0 cm^3, 2.0 mmol) in CH_2Cl_2 (3.0 cm^3) to make solution C, **374** (19 mg, 52%) was obtained as a clear oil. IR (film): 3356 (N–H), 1605 (C=C), 1348 (S=O), 1165 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.11 – 8.07 (1H, m, Ar*H*), 7.91 – 7.88 (1H, m, Ar*H*), 7.78 – 7.73 (2H, m, Ar*H*), 7.31 (2H, dd, *J* = 5.1, 8.6 Hz, Ar*H*), 7.02 (2H, t, *J* = 8.6 Hz, Ar*H*), 5.81 – 5.70 (1H, m, N*H*), 4.96 (1H, dd, *J* = 6.0, 7.9 Hz, ArC*H*), 3.70 – 3.63 (1H, m, CH*H*), 3.62 – 3.56 (1H, m, C*H*H); δ_C (125 MHz, $CDCl_3$): 162.9 (d, *J* = 249.0 Hz, (CF)), 147.9 (C), 134.0 (C), 133.8 (CH), 133.5 (d, *J* = 4.0 Hz, (C)), 133.1 (CH), 130.7 (CH), 129.1 (d, *J* = 8.0 Hz, (CH)), 125.6 (CH), 116.9 (d, *J* = 21.1 Hz, (CH)), 60.7 (CH), 51.1 (CH_2); *m/z* (ES^+) 381 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{14}H_{12}ClFN_2NaO_4S$ $[MNa]^+$: 381.0083, found: 381.0074.



375

***N*–[2–Ethoxy–2–(4–fluorophenyl)ethyl]–5–methylpyridine–2–sulfonamide, 375.** Using **343** (44 mg, 0.102 mmol) to make solution A; 4-fluorostyrene (62 mg, 0.508 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; H_2SO_4 (15 mg, 0.153 mmol) in EtOH (4.0 cm^3) to make solution C, **375** (21 mg, 61%) was obtained as a clear oil. IR (film): 3275 (N–H), 1604 (C=C), 1332 (S=O), 1171 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.54 – 8.50 (1H, m, Ar*H*), 7.88 – 7.84 (1H, m, Ar*H*), 7.70 – 7.65 (1H, m, Ar*H*), 7.21 (2H, dd, *J* = 5.6, 8.5 Hz, Ar*H*), 7.00 (2H, t, *J* = 8.5 Hz, Ar*H*), 5.32 (1H, dd, *J* = 3.2, 9.1 Hz, N*H*), 4.35 (1H, dd, *J* = 3.8, 9.2 Hz, ArC*H*), 3.40 – 3.24 (3H, m, OCH_2 and CH*H*), 3.10 – 3.03 (1H, m, C*H*H), 2.43 (3H, s, ArCH_3), 1.15 (3H, t, *J* = 7.0 Hz, OCH_2CH_3); δ_C (125 MHz, $CDCl_3$): 162.6 (d, *J* =

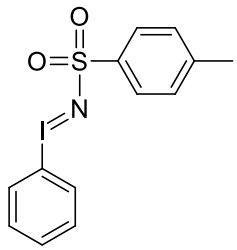
246.0 Hz, (CF)), 154.9 (C), 150.6 (CH), 138.1 (CH), 137.2 (C), 134.8 (d, *J* = 3.0 Hz, (C)), 128.2 (d, *J* = 8.0 Hz, (CH)), 121.7 (CH), 115.5 (d, *J* = 22.1 Hz, (CH)), 79.9 (CH), 64.5 (CH_2), 49.8 (CH_2), 18.5 (CH_3), 15.2 (CH_3); *m/z* (ES^+) 361 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{16}H_{19}FN_2NaO_3S$ $[MNa]^+$: 361.0993, found: 361.0993.



376

5-Methyl-2-[[4-(4-fluorophenyl)-2-methyl-4,5-dihydro-1*H*-imidazol-1-yl]sulfonyl]-pyridine, 376. Using **343** (44 mg, 0.102 mmol) to make solution A; 4-fluorostyrene (62 mg, 0.508 mmol) and $(pyr)_4Cu(OTf)_2$ (7 mg, 0.010 mmol) to make solution B; BF_3 (0.23 g of 15% BF_3 in MeCN solution; 0.52 mmol) in MeCN (4.0 cm^3) to make solution C, **376** (25 mg, 74%) was obtained as a clear oil. IR (film):1651, 1357 (S=O), 1174 (S=O) cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.55 – 8.49 (1H, m, Ar*H*), 7.92 – 7.88 (1H, m, Ar*H*), 7.75 – 7.70 (1H, m, Ar*H*), 7.13 (2H, dd, *J* = 5.3, 8.6 Hz, Ar*H*), 6.98 (2H, t, *J* = 8.6 Hz, Ar*H*); 5.07 – 5.00 (1H, m, ArC*H*), 4.27 (1H, t, *J* = 10.0 Hz, CH*H*), 3.67 (1H, dd, *J* = 8.0, 10.0 Hz, C*H*H), 2.46 (3H, s, ArCH_3), 2.44 – 2.42 (3H, m, CH_3); δ_C (125 MHz, $CDCl_3$): 162.2 (d, *J* = 246.1 Hz, (CF)), 157.4 (C), 153.6 (C), 150.7 (CH), 138.3 (CH), 138.2 (C), 137.7 (d, *J* = 3.0 Hz, (C)), 128.2 (d, *J* = 8.0 Hz, (CH)), 122.4 (CH), 115.5 (d, *J* = 21.1 Hz, (CH)) 66.3 (CH), 56.1 (CH_2), 18.6 (CH_3), 16.8 (CH_3); *m/z* (ES^+) 334 $[MH]^+$; HRMS (ES^+) calcd. for $C_{16}H_{17}FN_3O_2S$ $[MH]^+$: 334.1020, found: 334.1017.

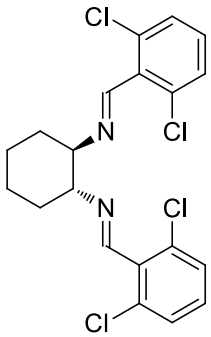
6.16 Synthesis of PhI=NTs



$TsNH_2$ (1.00 g, 5.84 mmol, 1 eq) and KOH (0.84 g, 15.0 mmol, 2.6 eq) were dissolved in MeOH (10 cm^3), and the solution cooled to 0 °C. $PhI(OAc)_2$ (1.88 g, 5.84 mmol, 1.0 eq) was added to the solution, and the mixture stirred at 0 °C for 10 min. The reaction mixture was then allowed to warm to room temperature and stirred for another 3 h, giving a yellow solution. H_2O (70 cm^3) was then added to the solution, and a pale yellow precipitate formed. The mixture was cooled to −78 °C to induce further precipitation.

Upon reaching room temperature, the precipitate was filtered off, washed with ^{n}hexane and dried under high vacuum to give PhI=NTs (1.55 g, 71%) as a pale yellow powder. M.p. 101 – 104 °C (decomposition); (lit. 102 – 104 °C). IR (film): 1561 (C=C), 1127 (S=O) cm^{-1}; δ_H (400 MHz, $(CD_3)_2SO$): 7.70 (2H, d, *J* = 7.7 Hz, Ar*H*), 7.46 (1H, t, *J* = 7.7 Hz, Ar*H*), 7.44 (2H, d, *J* = 7.9 Hz, Ar*H*), 7.30 (2H, t, *J* = 7.7 Hz, Ar*H*), 7.07 (2H, d, *J* = 7.9 Hz, Ar*H*), 2.28 (3H, s, ArCH_3); δ_H (100 MHz, $(CD_3)_2SO$): 142.7 (C), 140.5 (C), 133.7 (CH), 130.9 (CH), 130.6 (CH), 129.1 (CH), 126.6 (CH), 117.8 (C), 21.3 (CH_3). Data consistent with that reported in literature.[55]

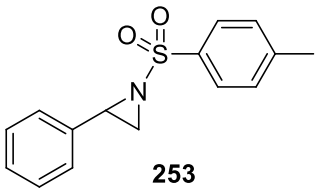
6.17 Synthesis of Jacobsen's chiral diimine ligand



67

***N,N'*-[(1*R*,2*R*)-Cyclohexane-1,2-diyl]*bis*[1-(2,6-dichloro phenyl)methanimine], 67.** (*1R,2R*)-cyclohexane-1,2-diamine (5.00 g, 43.8 mmol, 1 eq) and 2,6-dichloro benzaldehyde (15.3 g, 87.6 mmol, 2 eq) were dissolved in EtOH (350 cm^3) and heated to 100 °C with stirring for 1 h. The solution was cooled to room temperature, and a white solid crystallized out. The precipitate was filtered off, and dried under high vacuum to give **67** (15.19 g, 81%) as a white solid. M.p. 162 – 163 °C; (lit. 149 – 150 °C). IR (film): 2930 (C—H), 2855 (C—H), 1644, 1557 cm^{-1}; δ_H (500 MHz, $CDCl_3$): 8.47 (2H, s, ArC*H*), 7.27 (4H, d, *J* = 8.1 Hz, Ar*H*), 7.16 (2H, t, *J* = 8.1 Hz, Ar*H*), 3.65 – 3.56 (2H, m, (C=N)C*H*), 1.95 – 1.81 (6H, m, CH_2), 1.57 – 1.45 (2H, m, CH_2); δ_C (125 MHz. $CDCl_3$): 156.6 (CH), 134.9 (C), 132.9 (C), 130.0 (CH), 128.6 (CH), 75.0 (CH), 32.9 (CH_2), 24.3 (CH_2); *m/z* (ES^+) 427 $[MH]^+$; HRMS (ES^+) calcd. for $C_{20}H_{19}Cl_4N_2$ $[MH]^+$: 427.0297, found: 427.0297. Data consistent with that reported in literature.[60]

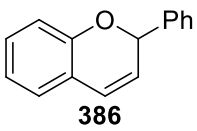
6.18 General procedure for enantioselective aziridinations with styrene



253

Styrene (0.50 mmol, 5.0 eq), $Cu^{I/II}$ catalyst (0.010 mmol, 0.1 eq) and chiral ligand (0.0125 mmol, 0.125 eq) were dissolved in solvent (1 cm^3), and the solution cooled to 0 °C. *N*-Tosyl aryliminoiodane (0.10 mmol, 1 eq) was added, and the solution stirred at 0 °C until all the aryliminoiodane had dissolved.[60,62] The solution was then loaded directly onto a column, and purified by gradient column chromatography (5:1 ^{n}hexane:EtOAc, then 3:1 ^{n}hexane:EtOAc) to give **253**. Enantioselectivity was determined by chiral HPLC (Daicel Chiralcel OJ, hexane:^{i}PrOH 7:3, 0.70 cm^3/min, 254 nm, 30 °C).

6.19 Synthesis of 2-phenyl-2*H*-chromene (386)

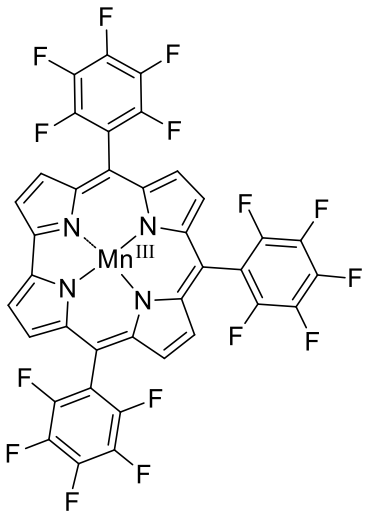


386

(*E*)-1-(2-Hydroxyphenyl)-3-phenylprop-2-en-1-one (5.00 g, 22.3 mmol, 1 eq) was dissolved in CH_2Cl_2 (200 cm^3), and $NaBH_4$ (2.54 g, 67.1 mmol, 3.0 eq) added. The mixture was stirred, and EtOH (20 cm^3) added, causing bubbles to form. After 3 h, more EtOH (200 cm^3) was added to quench any remaining $NaBH_4$, and stirred for 1 h. The solvent was removed on a rotary evaporator, and aq saturated NaCl (100 cm^3) added. The mixture was extracted with CH_2Cl_2 (5 × 20 cm^3), organic extracts combined, and dried with $MgSO_4$. To this solution was added AcOH (4 cm^3) dissolved in CH_2Cl_2 (16 cm^3), and the solution stirred at room temperature for 4 h.

The solution was then extracted with saturated aq NaCl (5 × 10 cm^3), and the organic layer dried with $MgSO_4$. The solvent was removed on a rotary evaporator to give an oil. This was purified by column chromatography (5:1 ^{n}hexane:CH_2Cl_2) to give **386** (2.88 g, 62%) as a clear oil. IR (film): 3028 (C—H), 1640, 1605 cm^{-1}, δ_H (500 MHz, $CDCl_3$): 7.45 (2H, d, *J* = 7.5 Hz, Ar*H*), 7.37 (2H, t, *J* = 7.5 Hz, Ar*H*), 7.32 (1H, t, *J* = 7.5 Hz, Ar*H*), 7.11 (1H, t, *J* = 7.6 Hz, Ar*H*), 7.01 (1H, d, *J* = 7.6 Hz, Ar*H*), 6.86 (1H, t, *J* = 7.6 Hz, Ar*H*), 6.79 (1H, d, *J* = 7.6 Hz, Ar*H*), 6.53 (1H, dd, *J* = 1.5, 9.9 Hz, C=C*H*), 5.93 – 5.90 (1H, m, PhC*H*), 5.80 (1H, dd, *J* = 3.5, 9.9 Hz, C=C*H*); δ_C (125 MHz, $CDCl_3$): 153.2 (C), 140.8 (C), 129.5 (CH), 128.7 (CH), 128.4 (CH), 127.0 (CH), 126.6 (CH), 124.9 (CH), 124.0 (CH), 121.3 (C), 121.2 (CH), 116.0 (CH), 77.2 (CH). Data consistent with that reported in literature.[286]

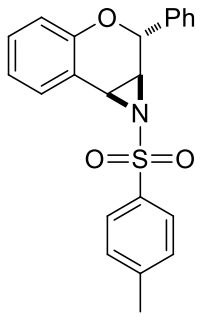
6.20 Synthesis of Manganese(III) 5,10,15-*tris*(pentafluorophenyl)corrole



Mn^{III}(TPFC)

CF_3SO_2H (1 cm^3) was dissolved in CH_2Cl_2 (10 cm^3). 100 μL of this solution was added to pentafluorobenzaldehyde (2.00 g, 10.2 mmol, 1 eq), and the mixture stirred at room temperature for 5 min. Pyrrole (1.03 g, 15.4 mmol, 1.5 eq) was then added, and the mixture quickly formed a tar. After stirring for 20 min, CH_2Cl_2 (100 cm^3) was added to dissolve the mixture, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.78 g, 12.2 mmol, 1.2 eq) dissolved in PhMe/THF (1:1, 10 cm^3) added. The mixture was stirred for another 10 min, then silica gel (100 cm^3) added. The mixture was stirred for another 5 min. The solvent was removed on a rotary evaporator, and the silica flushed with a mixture of CH_2Cl_2/^{n}hexane (1:2, 100 cm^3). The purple-black solution was then put on a rotary evaporator to remove organic solvents. The purple black solid which was obtained was dissolved in MeOH (50 cm^3), and $Mn(OAc)_2{\cdot}4H_2O$ (1.00 g, 4.1 mmol, 0.4 eq) added. The black solution was heated to 80 °C, and stirred for 3 h. The solvent was then removed on a rotary evaporator, CH_2Cl_2 (50 cm^3) added, and extracted with saturated aq NaCl (5 × 10 cm^3). The organic layer was dried with $MgSO_4$, solvent removed *in vacuo*, and purified by column chromatography (CH_2Cl_2/MeOH 100:1) to give Mn^{III}(TPFC) (38 mg, 1%) as a dark green-black solid. M.p. > 300 °C. IR (film): 1650, 1518, 1486, 1035 cm^{-1}; HRMS (ES$^+$) calcd. for $C_{37}H_8F_{15}MnN_4$ $[M]^{\cdot+}$: 847.9884, found: 847.9886; UV/Vis ($CHCl_3$): λ_{max} [nm] (lgε) = 397 (4.62), 416 (4.69), 480 (4.49), 599 (4.15). Data consistent with that reported in literature.[273-275]

6.21 Aziridination of 2-phenyl-2*H*-chromene

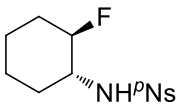


racemic **389**

2-Phenyl-1-tosyl-1,1a,2,7*b*-tetrahydrochromeno[3,4-*b*]azirine, 389. 2-Phenyl-2*H*-chromene (**386**) (100 mg, 0.48 mmol, 1 eq) was dissolved in MeCN (2 cm^3). $Cu(OTf)_2$ (17 mg, 0.047 mmol, 0.1 eq) was added, and the solution cooled to 0 °C. PhI=NTs (448 mg, 1.20 mmol, 2.5 eq) was added to the solution 0.5 eq at a time, only adding the next 0.5 eq when all the PhI=NTs had dissolved. After 3 h, the mixture was purified by column chromatography (^{n}hexane:EtOAc 5:1), giving **389** (9 mg, 5%) as a white solid. M.p. 190 – 192 °C. IR (film): 1596 (C=C), 1325 (S=O), 1158 (S=O) cm^{-1}, δ_H (500 MHz, CD_2Cl_2): 7.90 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.43 (2H, d, *J* = 8.3 Hz, Ar*H*), 7.37 – 7.28 (6H, m, Ar*H*), 7.25 (1H, t, *J* = 7.8 Hz, Ar*H*), 6.97 (1H, t, *J* = 7.8 Hz, Ar*H*), 6.80 (1H, d, *J* = 7.8 Hz, Ar*H*), 5.48 – 5.45 (1H, m, PhC*H*), 4.05 (1H, d, *J* = 7.3 Hz, NC*H*), 3.83 (1H, dd, *J* = 1.2, 7.3 Hz, NC*H*), 2.49 (3H, s, ArCH_3); δ_C (125 MHz, CD_2Cl_2): 152.1 (C), 145.2 (C), 137.5 (C), 135.0 (C), 130.6 (CH), 130.0 (CH), 129.4 (CH), 128.78 (CH), 128.76 (CH), 127.7 (CH), 127.0 (CH), 121.7 (CH), 118.5 (C), 118.0 (CH), 72.5 (CH), 45.3 (CH), 38.6 (CH), 21.4 (CH_3); *m/z* (ES^+) 400 $[MNa]^+$; HRMS (ES^+) calcd. for $C_{22}H_{19}NNaO_3S$ $[MNa]^+$: 400.0978, found: 400.0976.

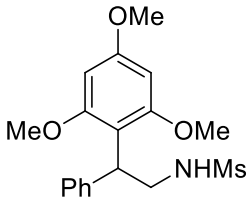
ArI=NTs **340** could also be used with similar yield to PhI=NTs, although the reaction with **340** occurred faster. It is not possible to accurately determine the diastereoselectivity as the crude ^{1}H NMR spectrum of **389** is complex.

6.22 X-ray crystallography



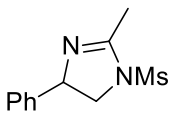
298

Crystal Data for **298**: $C_{12}H_{15}FN_2O_4S$ (M = 302.32 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 6.70613(9) Å, b = 8.92562(11) Å, c = 21.9646(3) Å, β = 91.7362(13)°, V = 1314.12(3) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 2.471 mm^{-1}, D_{calc} = 1.528 g/cm^3, 5727 reflections measured (8.054° ≤ 2Θ ≤ 157.56°), 2782 unique (R_{int} = 0.0239, R_{sigma} = 0.0330) which were used in all calculations. The final R_1 was 0.0402 (I > 2σ(I)) and wR_2 was 0.1104 (all data).



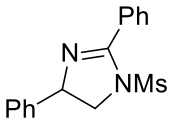
301

Crystal Data for **301**: $C_{18}H_{23}NO_5S$ (M = 365.43 g/mol): triclinic, space group P1 (no. 1), a = 8.6291(3) Å, b = 9.4332(3) Å, c = 12.4474(4) Å, α = 82.659(3)°, β = 70.506(3)°, γ = 68.236(3)°, V = 887.04(6) Å^3, Z = 2, T = 150.01(10) K, μ(CuKα) = 1.871 mm^{-1}, D_{calc} = 1.368 g/cm^3, 7775 reflections measured (7.534° ≤ 2Θ ≤ 157.94°), 4416 unique (R_{int} = 0.0299, R_{sigma} = 0.0416) which were used in all calculations. The final R_1 was 0.0436 (I > 2σ(I)) and wR_2 was 0.1167 (all data).



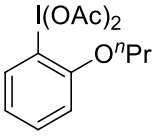
305

Crystal Data for **305**: $C_{11}H_{14}N_2O_2S$ (M = 238.30 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 15.2033(5) Å, b = 5.10542(13) Å, c = 15.6074(6) Å, β = 108.006(4)°, V = 1152.11(7) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 2.403 mm^{-1}, D_{calc} = 1.374 g/cm^3, 5511 reflections measured (7.094° ≤ 2Θ ≤ 156.968°), 2276 unique (R_{int} = 0.0287, R_{sigma} = 0.0338) which were used in all calculations. The final R_1 was 0.0372 (I > 2σ(I)) and wR_2 was 0.1081 (all data).



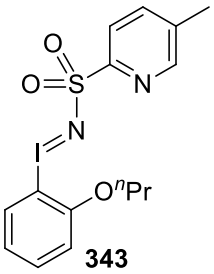
306

Crystal Data for **306**: $C_{16}H_{16}N_2O_2S$ (M = 300.37 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 8.2360(2) Å, b = 21.1919(5) Å, c = 8.4904(2) Å, β = 103.856(3)°, V = 1438.78(6) Å^3, Z = 4, T = 200(2) K, μ(CuKα) = 2.050 mm^{-1}, D_{calc} = 1.387 g/cm^3, 9198 reflections measured (8.344° ≤ 2Θ ≤ 157.522°), 3064 unique (R_{int} = 0.0455, R_{sigma} = 0.0497) which were used in all calculations. The final R_1 was 0.0448 (I > 2σ(I)) and wR_2 was 0.1278 (all data).



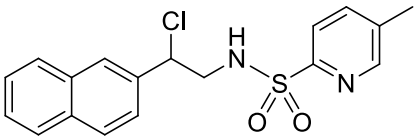
339

Crystal Data for **339**: $C_{13}H_{17}IO_5$ (M = 380.16 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 8.44405(16) Å, b = 12.0095(2) Å, c = 14.7747(3) Å, β = 91.8705(17)°, V = 1497.48(5) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 16.935 mm^{-1}, D_{calc} = 1.686 g/cm^3, 12604 reflections measured (9.492° ≤ 2Θ ≤ 157.332°), 3160 unique (R_{int} = 0.0516, R_{sigma} = 0.0319) which were used in all calculations. The final R_1 was 0.0343 (I > 2σ(I)) and wR_2 was 0.1022 (all data).



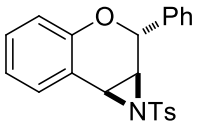
343

Crystal Data for **343**: $C_{15}H_{17}IN_2O_3S$ (M = 432.26 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 8.92490(6) Å, b = 12.07710(8) Å, c = 15.53550(13) Å, β = 98.2881(7)°, V = 1657.04(2) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 16.484 mm^{-1}, D_{calc} = 1.733 g/cm^3, 16679 reflections measured (9.312° ≤ 2Θ ≤ 156.092°), 3503 unique (R_{int} = 0.0323, R_{sigma} = 0.0198) which were used in all calculations. The final R_1 was 0.0302 (I > 2σ(I)) and wR_2 was 0.0816 (all data).



363

Crystal Data for **363**: $C_{18}H_{17}ClN_2O_2S$ (M = 360.84 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 11.48668(7) Å, b = 7.37203(6) Å, c = 20.25344(15) Å, β = 106.0333(7)°, V = 1648.35(2) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 3.347 mm^{-1}, D_{calc} = 1.454 g/cm^3, 32278 reflections measured (8.008° ≤ 2Θ ≤ 156.154°), 3520 unique (R_{int} = 0.0368, R_{sigma} = 0.0191) which were used in all calculations. The final R_1 was 0.0332 (I > 2σ(I)) and wR_2 was 0.0930 (all data).



389

Crystal Data for **389**: $C_{22}H_{19}NO_3S$ (M = 377.44 g/mol): monoclinic, space group $P2_1/n$ (no. 14), a = 6.18278(6) Å, b = 18.31757(16) Å, c = 16.08632(16) Å, β = 94.3033(10)°, V = 1816.69(3) Å^3, Z = 4, T = 150(2) K, μ(CuKα) = 1.771 mm^{-1}, D_{calc} = 1.380 g/cm^3, 34789 reflections measured (7.326° ≤ 2Θ ≤ 147.312°), 3652 unique (R_{int} = 0.0502, R_{sigma} = 0.0200) which were used in all calculations. The final R_1 was 0.0326 (I > 2σ(I)) and wR_2 was 0.0845 (all data).

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